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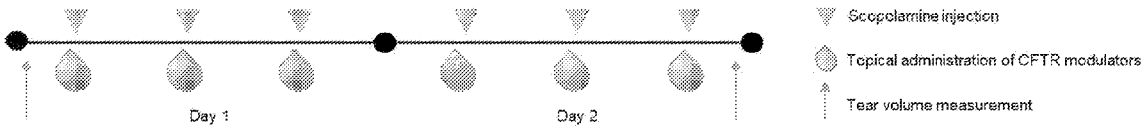

FIG. 1

(57) Abstract: The present disclosure provides methods of using CFTR modulator compounds and compositions including said compounds for modulating CFTR, methods for treating an eye disease or disorder, and methods for treating CFTR-related indications. The present disclosure also provides methods of using PDE4 inhibiting compounds and compositions including said compounds for inhibiting PDE4. In some embodiments, the PDE4 inhibitor compounds of this disclosure are anti-inflammatory compounds capable of activation of target CFTR. The present disclosure also provides methods of using said compounds and compositions for treating an inflammatory disease or disorder, and methods for treating PDE4-related indications.

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USES OF CFTR MODULATOR AND/OR PDE4 INHIBITOR COMPOUNDS

1. CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/270,741, filed October 22, 2021, which is hereby incorporated in its entirety by reference.

2. INTRODUCTION

[0002] Cystic fibrosis transmembrane conductance regulator (CFTR) is a membrane protein encoded by the *CFTR* gene and codes for an ABC transporter-class ion channel protein that conducts chloride ions across cell membranes. Certain mutations of the CFTR gene can negatively affect chloride ion channel function, leading to dysregulation of epithelial fluid transport in many organs, such as the lung and the pancreas, resulting in cystic fibrosis. Furthermore, wild-type CFTR proteins can be modulated by a direct activation mechanism, but its inappropriate activation can lead to secretory diarrheas such as cholera.

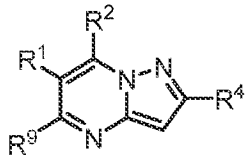
[0003] Activators of wild-type CFTR are of interest for use in clinical indications for prosecretory therapy of constipation and dry eye disorders and for disorders of the liver, pancreas, and airways. CFTR inhibitors are of interest for treating certain secretory diarrheas and polycystic kidney disease.

[0004] Phosphodiesterase 4 (PDE4) is a key enzyme responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP), an intracellular messenger that controls a variety of proinflammatory and anti-inflammatory mediators. Increased intracellular cAMP levels can result from the inhibition of PDE4, and have significant anti-inflammatory effects by blocking the recruitment of immune cells and the release of proinflammatory mediators. Hematopoietic cells such as dendritic cells, T cells, macrophages, and monocytes are controlled by PDE4.

3. SUMMARY

[0005] The present disclosure provides methods of using CFTR modulator compounds and compositions including said compounds for modulating CFTR, methods for treating an eye disease or disorder, and methods for treating CFTR-related indications. The present disclosure also provides methods of using PDE4 inhibiting compounds and compositions including said compounds for inhibiting PDE4. In some embodiments, the PDE4 inhibitor compounds of this disclosure are anti-inflammatory compounds capable of activation of target CFTR. The present disclosure also provides methods of using said compounds and compositions for treating an inflammatory disease or disorder, and methods for treating PDE4-related indications.

[0006] In a first aspect of the methods of this disclosure, the compound is of formula (Ia):



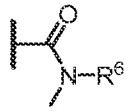
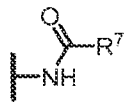
(Ia)

,

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

R^9 is selected from H and halogen.

[0007] In another aspect, the present disclosure provides a method of treating dry eye disease or CFTR-related indications, including administering to an eye of a subject a therapeutically effective amount of a compounds and/or an ophthalmic composition as described herein (e.g., a composition including a compound of formula (Ia)-(Ie), as described herein). In some embodiments, the method of treating dry eye disease further includes identifying a subject suffering from dry eye disease, or identifying an underlying disease or condition associated with the dry eye disease. In some

embodiments, the subject may be a human subject having dry eye diseases or symptoms, or CFTR-related indications.

[0008] In another aspect, the present disclosure provides a method of treating an inflammatory disease or PDE4-related indications, including administering to a subject a therapeutically effective amount of a PDE4 inhibiting compound (e.g., a compound of formula (Ia)-(Ie), as described herein), or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, or a pharmaceutical composition including the same. In some embodiments, the subject may be a human subject having an inflammatory disease or a PDE4-related indication.

4. BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0009] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

[0010] FIG. 1 shows the study schedule of *in vivo* mouse model with decreased tear volume.

[0011] FIG. 2 shows the results for TNF-alpha in human peripheral blood mononuclear cells (PBMCs).

[0012] FIG. 3 shows the results for IFN-gamma in human PBMCs.

[0013] FIG. 4 shows the results for CCL3/MIP-1 alpha in human PBMCs.

[0014] FIG. 5 shows the cell viability measured for various subject compounds in human PBMCs by CCK-8 assay.

[0015] Significance levels for FIGs 2-5 are as follows: *p<0.05, **p<0.01, ***p<0.001 Control group vs All group; #p<0.05, ##p<0.01, ###p<0.001 LPS group vs All group; &p<0.05, &&p<0.01, &&&p<0.001 Apremilast group vs All group; $p<0.05, $$p<0.01, $$$p<0.001 Xiidra group vs All group.

[0016] FIGs. 6A-6D shows the severity of psoriasis-like inflammation scores for the imiquimod-induced psoriasis mouse model. FIG. 6A shows the total PASI score for various subject compounds at day 9. FIG. 6B shows the erythema score for various subject compounds at day 9. FIG. 6C shows the thickness score for various subject compounds at day 9. FIG. 6D shows the skin plaque (scales) score for various subject compounds at day 9.

[0017] FIGs. 7A-7D shows the severity of psoriasis-like inflammation scores for compound 41 in the imiquimod-induced psoriasis mouse model. FIG. 7A shows the erythema score for compound 41 from day 0-9. FIG. 7B shows the thickness score for compound 41 from day 0-9. FIG. 7C shows the skin plaque (scales) score for compound 41 from day 0-9. FIG. 7D shows the total PASI score for compound 41 from day 0-9.

[0018] FIGs. 8A-8D shows the severity of psoriasis-like inflammation scores for compound 205 in the imiquimod-induced psoriasis mouse model. FIG. 8A shows the erythema score for compound 205 from day 0-9. FIG. 6B shows the thickness score for compound 205 from day 0-9. FIG. 6C shows the

skin plaque (scales) score for compound 205 from day 0-9. FIG. 6D shows the total PASI score for compound 205 from day 0-9.

[0019] FIGs. 9A-9D shows the severity of psoriasis-like inflammation scores for compound 144 in the imiquimod-induced psoriasis mouse model. FIG. 8A shows the erythema score for compound 144 from day 0-9. FIG. 8B shows the thickness score for compound 144 from day 0-9. FIG. 8C shows the skin plaque (scales) score for compound 144 from day 0-9. FIG. 8D shows the total PASI score for compound 144 from day 0-9.

[0020] FIGs. 10A-10D shows the severity of psoriasis-like inflammation scores for compound 3 in the imiquimod-induced psoriasis mouse model. FIG. 10A shows the erythema score for compound 3 from day 0-9. FIG. 10B shows the thickness score for compound 3 from day 0-9. FIG. 10C shows the skin plaque (scales) score for compound 3 from day 0-9. FIG. 10D shows the total PASI score for compound 3 from day 0-9.

[0021] FIGs. 11A-11D shows the severity of psoriasis-like inflammation scores for compound 257 in the imiquimod-induced psoriasis mouse model. FIG. 11A shows the erythema score for compound 257 from day 0-9. FIG. 11B shows the thickness score for compound 257 from day 0-9. FIG. 11C shows the skin plaque (scales) score for compound 257 from day 0-9. FIG. 11D shows the total PASI score for compound 257 from day 0-9.

[0022] FIGs. 12A-12D shows the severity of psoriasis-like inflammation scores for compound 15 in the imiquimod-induced psoriasis mouse model. FIG. 12A shows the erythema score for compound 15 from day 0-9. FIG. 12B shows the thickness score for compound 15 from day 0-9. FIG. 12C shows the skin plaque (scales) score for compound 15 from day 0-9. FIG. 12D shows the total PASI score for compound 15 from day 0-9.

[0023] FIGs. 13A-13D shows the severity of psoriasis-like inflammation scores for compound 352 in the imiquimod-induced psoriasis mouse model. FIG. 13A shows the erythema score for compound 352 from day 0-9. FIG. 13B shows the thickness score for compound 352 from day 0-9. FIG. 13C shows the skin plaque (scales) score for compound 352 from day 0-9. FIG. 13D shows the total PASI score for compound 352 from day 0-9.

[0024] FIG. 14 shows representative histological image of a normal skin tissue sample.

[0025] FIG. 15 shows representative histological image of a skin tissue sample treated with IMQ (imiquimod) cream.

[0026] FIG. 16 shows representative histological image of a skin tissue sample treated with IMQ and a vehicle.

[0027] FIG. 17 shows representative histological image of a skin tissue sample treated with IMQ and compound 41.

[0028] FIG. 18 shows representative histological image of a skin tissue sample treated with IMQ and compound 205.

[0029] FIG. 19 shows representative histological image of a skin tissue sample treated with IMQ and compound 144.

[0030] FIG. 20 shows representative histological image of a skin tissue sample treated with IMQ and compound 3.

[0031] FIG. 21 shows representative histological image of a skin tissue sample treated with IMQ and compound 257.

[0032] FIG. 22 shows representative histological image of a skin tissue sample treated with IMQ and compound 15.

[0033] FIG. 23 shows representative histological image of a skin tissue sample treated with IMQ and compound 352.

[0034] FIG. 24 shows the epidermal thickness changes in the IMQ-induced psoriasis tissue samples treated with various subject compounds.

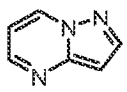
[0035] FIG. 25 shows the dermal thickness changes in the IMQ-induced psoriasis tissue samples treated with various subject compounds.

[0036] FIG. 26 shows the changes in the number of inflammatory cells/mm^2 in the IMQ-induced psoriasis tissue samples treated with various subject compounds.

5. DETAILED DESCRIPTION

5.1. CFTR Modulator and/or PDE4 Inhibitor Compounds

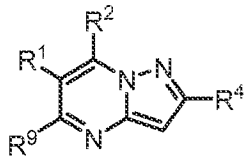
[0037] As summarized above, the present disclosure provides compounds and compositions for use in modulating CFTR. Also provided are compounds and compositions for use inhibiting PDE4. In some embodiments, the compounds of this disclosure have CFTR modulating and/or PDE4 inhibiting activity. In some embodiments, the PDE4 inhibitor compounds of this disclosure are anti-inflammatory compounds capable of activation of target CFTR.

[0038] The compounds can include a fused bicyclic core structure of pyrazolo[1,5-a]pyrimidine ().

[0039] In the compounds of the present disclosure, compounds containing the pyrazolo[1,5-a]pyrimidine core can be substituted at the 2 position of the core structure with optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle substituents, at the 5 position of the core structure with halogen, at the 6 position of the core structure with halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy substituents, and at the 7 position of the core structure with optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle. In various embodiments as described herein, the optionally substituted substituents at the one or more positions of the core

structure may optionally be further substituted. Compounds having such substituted pyrazolo[1,5-a]pyrimidine core structure as described herein can have desirable CFTR modulating and PDE4 inhibiting activities and find use in a variety of applications.

[0040] Accordingly, in a first aspect, the present disclosure provides a compound of formula (Ia):

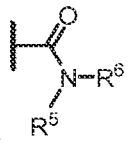
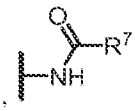
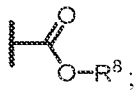


(Ia)

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from optionally substituted H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

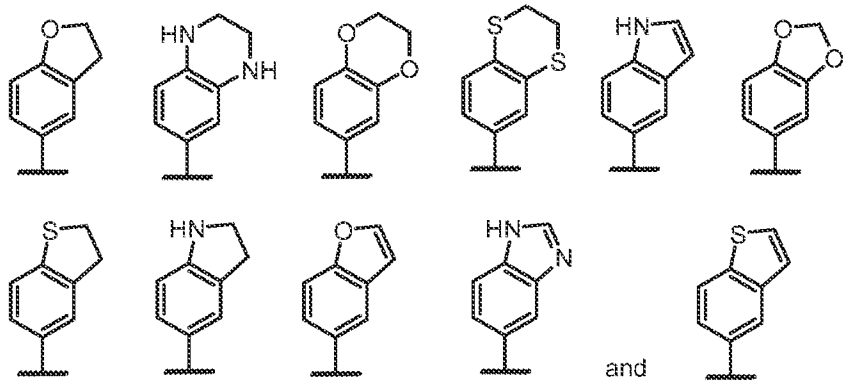
R^9 is selected from H and halogen.

[0041] In some embodiments of formula (Ia), R^2 is a substituted aryl. In certain cases, R^2 is a mono-substituted aryl. In certain cases, R^2 is a di-substituted aryl. In certain cases, R^2 is a tri-substituted aryl. In certain cases, the substituents in the di-substituted aryl or the tri-substituted aryl are adjacent one another. In certain cases, the di-substituted aryl is a 2,3-di-substituted aryl. In certain cases, the

di-substituted aryl is a 3,4-di-substituted aryl. In certain cases, the di-substituted aryl is a 4,5-di-substituted aryl. In certain cases, the di-substituted aryl is a 5,6-di-substituted aryl. In certain cases, the di-substituted aryl is a 2,4-di-substituted aryl. In certain cases, the di-substituted aryl is a 2,5-di-substituted aryl. In certain cases, the di-substituted aryl is a 2,6-di-substituted aryl. In certain cases, the di-substituted aryl is a 3,5-di-substituted aryl. In certain cases, the di-substituted aryl is a 3,6-di-substituted aryl. In certain cases, the di-substituted aryl is a 4,6-di-substituted aryl. In certain cases, the tri-substituted aryl is a 2,3,4-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 3,4,5-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 4,5,6-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 2,3,5-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 2,3,6-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 2,4,5-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 2,4,6-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 2,5,6-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 3,4,6-tri-substituted aryl. In certain cases, the tri-substituted aryl is a 3,5,6-tri-substituted aryl.

[0042] In some embodiments of formula (Ia), R^2 is an optionally substituted heteroaryl. In another embodiment, R^2 is selected from optionally substituted furanyl (e.g., 2-furanyl) and optionally substituted thiophene (e.g., 2-thiopheneyl). In another embodiment, R^2 is an optionally substituted benzo fused heterocycle.

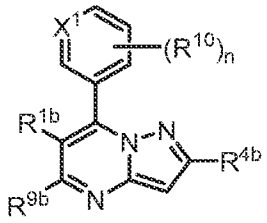
[0043] In some embodiments of formula (Ia), R^2 is a heterocycle selected from:



[0044] In some embodiments of formula (Ia), R^2 is an optionally substituted phenyl or an optionally substituted heteroaryl. In certain cases, R^2 is a substituted phenyl with 1 to 3 substituents or a substituted heteroaryl with 1 to 3 substituents. In certain cases, R^2 is a 3-substituted phenyl. In certain cases, R^2 is a 4-substituted phenyl. In certain cases, R^2 is a di-substituted phenyl. In certain cases, the substituents on the di-substituted phenyl are adjacent one another. In certain cases, the di-substituted phenyl is a 2,3-di-substituted phenyl. In certain cases, the di-substituted phenyl is a 3,4-disubstituted phenyl. In certain cases, the di-substituted phenyl is a 4,5-di-substituted phenyl. In certain cases, the di-substituted phenyl is a 5,6-di-substituted phenyl. In certain cases, the di-substituted phenyl is a 2,4-di-substituted phenyl. In certain cases, the di-substituted phenyl is a 2,5-di-substituted phenyl. In certain cases, the di-substituted phenyl is a 2,6-di-substituted phenyl. In certain

cases, the di-substituted phenyl is a 3,5-di-substituted phenyl. In certain cases, the di-substituted phenyl is a 3,6-di-substituted phenyl. In certain cases, the di-substituted phenyl is a 4,6-di-substituted phenyl. In certain cases, R^2 is a tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 2,3,4-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 3,4,5-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 4,5,6-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 2,3,5-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 2,3,6-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 2,4,5-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 2,4,6-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 2,5,6-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 3,4,6-tri-substituted phenyl. In certain cases, the tri-substituted phenyl is a 3,5,6-tri-substituted phenyl.

[0045] In some embodiments of formula (Ia), where R^2 is an optionally substituted phenyl or an optionally substituted heteroaryl, the compound is of formula (Ib):

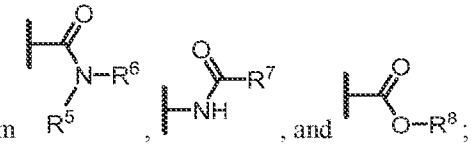


(Ib)

wherein:

X^1 is $CR^{10'}$ or N;

R^{1b} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4b} is selected from  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

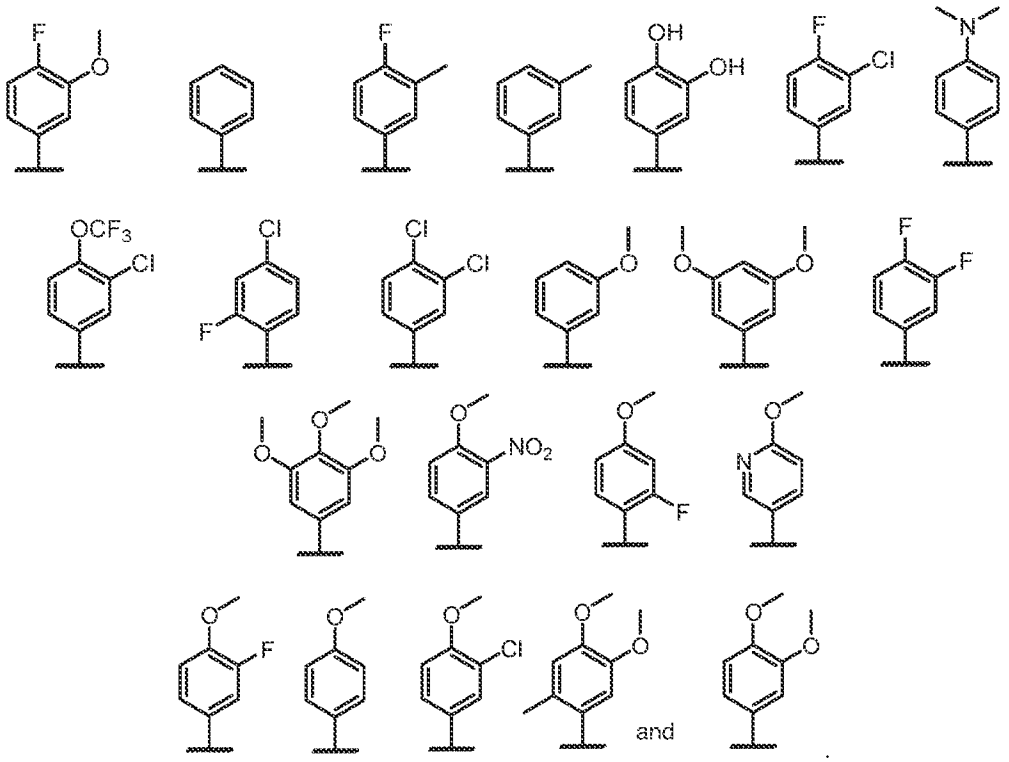
R^{9b} is selected from H and halogen;

each R^{10} and $R^{10'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

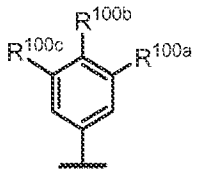
n is 0 to 4.

[0046] In some embodiments of the compound of formula (Ib), each R^{10} and $R^{10'}$ is independently selected from H, OH, CH_3, CF_3, OCF_3, OCH_3, NO_2, F, Cl, and dimethylamine.

[0047] In some embodiments of formula (Ia) or (Ib), R^2 is selected from:



[0048] In some embodiments of formula (Ia), R^2 is:

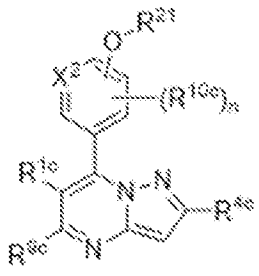


wherein:

each R^{100a}-R^{100c} is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and at least one of R^{100a}, R^{100b} and R^{100c} is not H. In certain embodiments, R^{100a}-R^{100c} are independently selected from H, NO_2, halogen, optionally substituted (C_1-C_3)alkyl, and optionally substituted (C_1-C_3)alkoxy. In certain embodiments, each of R^{100a}-R^{100c} is a different group. In certain embodiments, each of R^{100a}-R^{100c} is different and independently selected from H, halogen, NO_2, methoxy and methyl. In certain embodiments, each of $R^{100a}R^{100c}$ is the same, and is not H. In certain cases, each of R^{100a}-R^{100c} is (C_1-

C_3)alkoxy. In certain cases, each of R^{100a}-R^{100c} is methoxy. In certain cases, two of R^{100a}-R^{100c} are (C_1-C_3)alkoxy, and the other one of R^{100a}-R^{100c} is H. In certain cases, two of R^{100a}-R^{100c} are methoxy, and the other one of R^{100a}-R^{100c} is H. In certain cases, each of R^{100a} and R^{100b} (C_1-C_3)alkoxy, and R^{100c} is H. In certain cases, each of R^{100a} and R^{100b} are methoxy, and R^{100c} is H.

[0049] In some embodiments of formula (Ib), the compound is of formula (Ic):



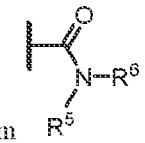
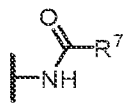
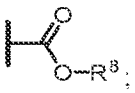
(Ic)

wherein:

X^2 is $CR^{10c'}$ or N;

R^{21} is selected from H, and optionally substituted (C_1-C_{10})alkyl; optionally substituted acyl; optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{1c} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4c} is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

R^{9c} is selected from H and halogen;

each R^{10c} and $R^{10c'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally

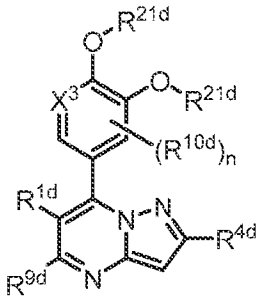
substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 3.

[0050] In some embodiments of formula (Ic), R^{21} is H, or optionally substituted (C_1-C_6)alkyl. In some embodiments of formula (Ic), R^{21} is (C_1-C_6)alkyl. In some embodiments of formula (Ic), R^{21} is methyl.

[0051] In some embodiments of formula (Ic), -O-R^{21} is connected to the phenyl ring at the para-position. In some embodiments of formula (Ic), -O-R^{21} is connected to the phenyl ring at the meta-position.

[0052] In certain embodiments of formula (Ic), the compound is of formula (Id):



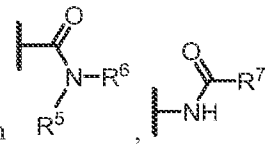
(Id)

wherein:

X^3 is $CR^{10d'}$ or N;

each R^{21d} is independently selected from H, and optionally substituted (C_1-C_{10})alkyl; optionally substituted acyl; optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{1d} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4d} is selected from  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

R^{9d} is selected from H and halogen;

each R^{10d} and $R^{10d'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 2.

[0053] In some embodiments of formula (Id), each R^{21d} is independently H, or optionally substituted (C_1-C_6)alkyl. In some embodiments of formula (Id), each R^{21d} is independently (C_1-C_6)alkyl. In some embodiments of formula (Id), each R^{21d} is methyl.

[0054] In certain embodiments of formula (Id), X^3 is $CR^{10d'}$. In certain embodiments of formula (Id), X^3 is CH. In certain embodiments of formula (Id), X^3 is $CR^{10d'}$, where $R^{10d'}$ is - optionally substituted (C_1-C_6)alkoxy. In certain embodiments of formula (Id), X^3 is $CR^{10d'}$, where $R^{10d'}$ is -OCH_3. In certain embodiments of formula (Id), $R^{10d'}$ is -OCH_3 and n is 0.

[0055] In certain embodiments of formula (Id), X^3 is N.

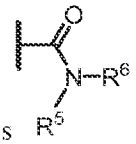
[0056] In certain embodiments of formula (Id), X^3 is $CR^{10d'}$. In certain embodiments of formula (Id), X^3 is $CR^{10d'}$, n is 0. In certain embodiments of formula (Id), X^3 is $CR^{10d'}$, and n is 1. In certain embodiments of formula (Id), when n is 1 or 2, each R^{10d} is independently selected from halogen, and optionally substituted (C_1-C_6)alkyl.

[0057] In certain embodiments of formula (Id), each R^{21d} is optionally substituted (C_1-C_6)alkyl, X^3 is $CR^{10d'}$, n is 0 or 1, and R^{10d} and $R^{10d'}$ are independently optionally substituted (C_1-C_6)alkyl or halogen.

[0058] In certain embodiments of formula (Id), each R^{21d} is methyl, X^3 is $CR^{10d'}$, where $R^{10d'}$ is -OCH_3, and n is 0.

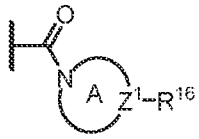
[0059] In certain embodiments of formula (Id), each R^{21d} is optionally substituted (C_1-C_6)alkyl, X^3 is CH, n is 1, and R^{10d} is optionally substituted (C_1-C_6)alkyl or halogen. In certain embodiments of formula (Id), each R^{21d} is methyl, X^3 is CH, and n is 1 where the R^{10d} is methyl located at the ortho position.

[0060] In some embodiments of formula (Id), each R^{21d} is methyl, and n is 0.

[0061] In some embodiments of formula (Ia)-(Id), any of R^4-R^{4d} is  .

In some embodiments of formula (Ia)-(Id), R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to provide an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle.

[0062] In some embodiments of formula (Ia)-(Id), any of R^4-R^{4d} is



wherein:

ring A is an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle;

Z^1 is CR^{14} or N, where R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle; and

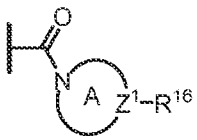
R^{16} is selected from H, halogen, $-OR^{22a}$, $-C(O)R^{22b}$, $-CO_2R^{22c}$, and $-C(O)NR^{50}R^{60}$, $-NR^{50}R^{60}$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^{22a}, R^{22b}, and R^{22c} are independently selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

R^{50} and R^{60} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

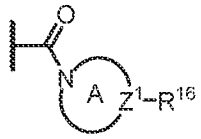
or R^{50} and R^{60} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted heterocycle, or an optionally substituted heteroaryl.

[0063] In some embodiments of formula (Ia)-(Id) when any of R^4-R^{4d} is

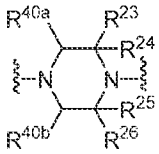


and the A ring is piperidine, then R^{16} comprises at least one cyclic group selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle. In some cases, the A ring is piperidine and R^{16} comprises an optionally substituted aryl. In some cases, the optionally substituted aryl is optionally substituted phenyl. In some cases, the A ring is piperidine and R^{16} comprises an optionally substituted heteroaryl. In some cases, the A ring is piperidine and R^{16} comprises an optionally substituted carbocycle. In some cases, the A ring is piperidine and R^{16} comprises an optionally substituted heterocycle.

[0064] In some embodiments of formula (Ia)-(Id) when any of R^4-R^{4d} is



, the A ring is an optionally substituted piperazine, pyrrolidine, or azetidine. In certain cases, the A ring is:



wherein:

R^{23}-R^{26} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; or

one or both of R^{23}-R^{24} and R^{25}-R^{26} together with the carbon atom to which they are attached are cyclically linked to form an optionally substituted carbocycle or an optionally substituted heterocycle; and

R^{40a} and R^{40b} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle.

[0065] In some embodiments, R^{23} is selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and R^{24}-R^{26}, R^{40a} and R^{40b} are each H. In certain cases, R^{23} is selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases, R^{23} is methyl. In certain cases, R^{23} is ethyl. In certain cases, R^{23} is propyl. In certain cases, R^{23} is isopropyl. In some embodiments, R^{23} is (C_1-C_6)cycloalkyl. In certain cases, R^{23} is cyclopropyl. In certain cases, R^{23} is cyclobutyl. In certain cases, R^{23} is cyclopentyl. In certain cases, R^{23} is cyclohexyl.

[0066] In certain embodiments of the A ring, two of R^{23}, R^{25}, and R^{40b} are independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and the other one of R^{23}, R^{25} and R^{40b} is H, and R^{24}, R^{26} and R^{40a} are each H. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are optionally substituted (C_1-C_6)alkyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are each independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are methyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are ethyl. In certain cases, two of R^{23}, R^{25}, and R^{40b} are propyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are isopropyl. In some embodiments of the A ring, two of R^{23}, R^{25}, and R^{40b} are (C_1-C_6)cycloalkyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are cyclopropyl. In certain cases, two of R^{23}, R^{25}, and R^{40b} are cyclobutyl. In certain cases of the A ring,

two of R^{23}, R^{25}, and R^{40b} are cyclopentyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are cyclohexyl.

[0067] In certain embodiments of the A ring, R^{23} and R^{25} are each independently selected from optionally substituted (C_1-C_6)alkyl, and optionally substituted cycloalkyl; and R^{24}, R^{26} and R^{40a}-R^{40b} are each H. In certain cases of the A ring, both R^{23} and R^{25} are optionally substituted (C_1-C_6)alkyl. In certain cases of the A ring, R^{23} and R^{25} are each independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases of the A ring, both R^{23} and R^{25} are methyl. In certain cases of the A ring, both R^{23} and R^{25} are ethyl. In certain cases of the A ring, both R^{23} and R^{25} are propyl. In certain cases of the A ring, both R^{23} and R^{25} are isopropyl. In some embodiments of the A ring, both R^{23} and R^{25} are (C_1-C_6)cycloalkyl. In certain cases of the A ring, both R^{23} and R^{25} are cyclopropyl. In certain cases, both R^{23} and R^{25} are cyclobutyl. In certain cases of the A ring, both R^{23} and R^{25} are cyclopentyl. In certain cases of the A ring, both R^{23} and R^{25} are cyclohexyl.

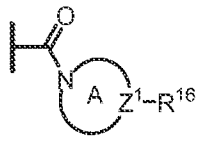
[0068] In certain embodiments of the A ring, R^{23} and R^{40b} are each independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and R^{24}-R^{26} and R^{40a} are each H. In certain cases, both R^{23} and R^{40b} are optionally substituted (C_1-C_6)alkyl. In certain cases, R^{23} and R^{40b} are each independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases, both R^{23} and R^{40b} are methyl. In certain cases, both R^{23} and R^{40b} are ethyl. In certain cases, both R^{23} and R^{40b} are propyl. In certain cases, both R^{23} and R^{40b} are isopropyl. In some embodiments, both R^{23} and R^{40b} are (C_1-C_6)cycloalkyl. In certain cases, both R^{23} and R^{40b} are cyclopropyl. In certain cases, both R^{23} and R^{40b} are cyclobutyl. In certain cases, both R^{23} and R^{40b} are cyclopentyl. In certain cases, both R^{23} and R^{40b} are cyclohexyl.

[0069] In certain embodiments of the A ring, R^{23} and R^{24} are each independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and R^{25}-R^{26}, R^{40a} and R^{40b} are each H. In certain cases, both R^{23} and R^{24} are optionally substituted (C_1-C_6)alkyl. In certain cases, R^{23} and R^{24} are each independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases, both R^{23} and R^{24} are methyl. In certain cases, both R^{23} and R^{24} are ethyl. In certain cases, both R^{23} and R^{24} are propyl. In certain cases, both R^{23} and R^{25} are isopropyl. In some embodiments, both R^{23} and R^{24} are (C_1-C_6)cycloalkyl. In certain cases, both R^{23} and R^{24} are cyclopropyl. In certain cases, both R^{23} and R^{24} are cyclobutyl. In certain cases, both R^{23} and R^{24} are cyclopentyl. In certain cases, both R^{23} and R^{24} are cyclohexyl.

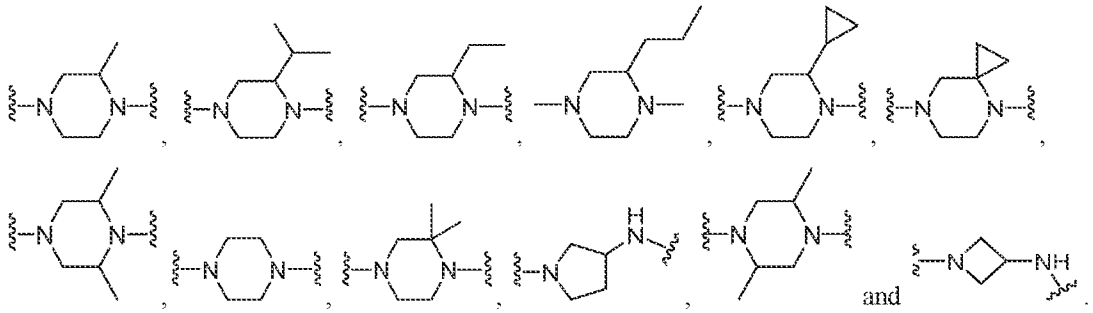
[0070] In certain embodiments of the A ring, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a carbocycle; and R^{25}-R^{26}, R^{40a} and R^{40b} are each H. In some embodiments, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a (C_1-C_6)cycloalkyl. In certain cases, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a cyclopropyl. In certain cases, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a

cyclobutyl. In certain cases, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a cyclopentyl. In certain cases, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a cyclohexyl.

[0071] In some embodiments of formula (Ia)-(Id) when any of R^4-R^{4d} is:



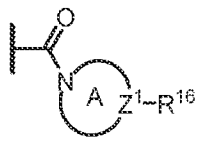
, the A ring is selected from:



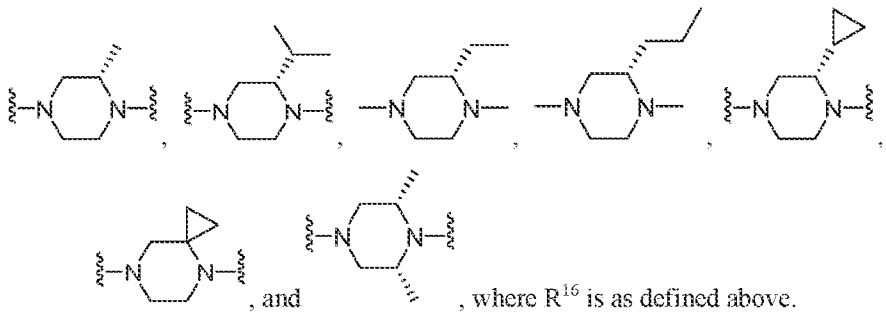
and .

In some embodiments, R^{16} is selected from H, halogen, $-OR^{22a}$, $-C(O)R^{22b}$, $-CO_2R^{22c}$, and $-C(O)NR^{50}R^{60}$, $-NR^{50}R^{60}$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, where R^{22a}, R^{22b}, R^{22c}, R^{50}, and R^{60} are as defined above.

[0072] In some embodiments of formula (Ia)-(Id) when any of R^4-R^{4d} is:

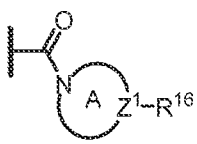


, the A ring is selected from:



, and , where R^{16} is as defined above.

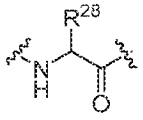
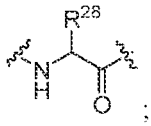
[0073] In some embodiments of formula (Ia)-(Id) any of R^4-R^{4d} is



, wherein R^{16} is:

$$-(R^{110})_nR^{210}$$

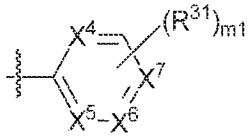
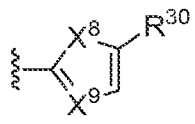
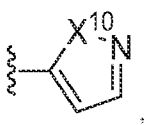
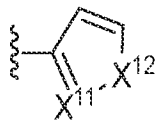
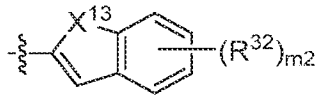
wherein:

each R^{110} is independently selected from optionally substituted (C_1-C_6)alkyl,  , -C(O)(R^{110a})n^1, -C(O)O(R^{110b})n^2, -S(O)(R^{110c})n^3, -SO_2(R^{110d})n^4, and -C(O)NR^{27}(R^{110e})n^5; where R^{110a}-R^{110e} are each independently optionally substituted (C_1-C_6)alkyl,  ; R^{27}-R^{28} are each independently selected from H and optionally substituted (C_1-C_6)alkyl; and n-n^5 are each independently 0 to 3; and

R^{210} is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle.

[0074] In some embodiments, R^{110} is selected from -C(O)-, -C(O)O-, -C(O)NH-, -S(O)-, and -SO_2-; and R^{210} is selected from optionally substituted aryl and optionally substituted heteroaryl. In certain embodiments, R^{110} is -C(O)- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -C(O)O- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -C(O)NH- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -S(O)- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -SO_2- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -C(O)- and R^{210} is optionally substituted heteroaryl. In certain embodiments, R^{110} is -C(O)O- and R^{210} is optionally substituted heteroaryl. In certain embodiments, R^{110} is -C(O)NH- and R^{210} is optionally substituted heteroaryl. In certain embodiments, R^{110} is -S(O)- and R^{210} is optionally substituted heteroaryl. In certain cases, R^{110} is -SO_2- and R^{210} is optionally substituted heteroaryl.

[0075] In some embodiments, R^{210} is selected from:

 ,  ,  ,  , and  , wherein:

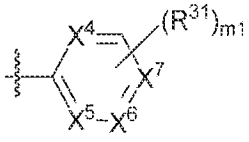
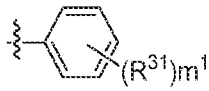
X^4-X^7, X^9, and X^{11} are each independently selected from CH, CR^{31}, S, O, and N;

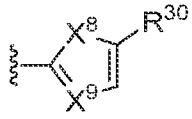
X^8, X^{10}, X^{12} and X^{13} are each independently selected from S, O, and NR^{29};

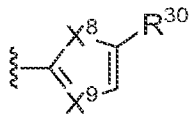
R^{29} is selected from H and optionally substituted (C_1-C_6)alkyl;

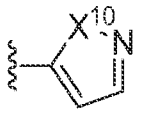
R^{30}-R^{32} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

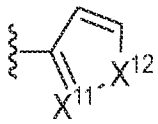
m^1-m^2 are each independently 0 to 5.

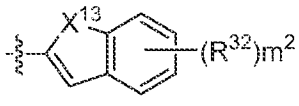
[0076] In some embodiments, R^{210} is  , where X^4-X^7 are each independently selected from CH, CR^{31}, S, O, and N. In some embodiments, R^{210} is  .

[0077] In some embodiments, R^{210} is  where X^9 is selected from CH, CR^{31}, S, O, and N; and X^8 is selected from S, O, and NR^{29}. In some cases, R^{29} is methyl. In some embodiments of R^{210} is X^9 is CH, CR^{31}, S, O, and N; and X^8 is selected from S, O, and NR^{29}. In some cases, X^9 is CH, and X^8 is S. In some cases, R^{30} is H. In some cases, R^{30} is methyl. In some embodiments, X^9 is CH, X^8 is S, and R^{30} is H. In some cases, X^9 is CH, X^8 is NR^{29}, and R^{30} is H. In some cases, X^9 is CH, and X^8 is NH. In some cases, X^9 is CH, X^8 is O and R^{30} is $(C_1$-$C_6)$alkyl. In some cases, X^9 is CH, X^8 is O and R^{30} is methyl.

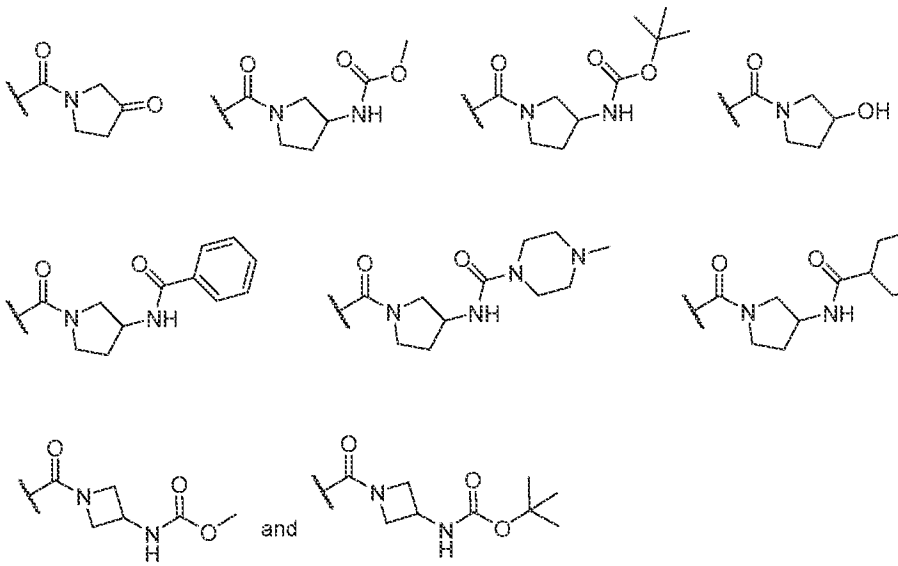
[0078] In some embodiments, R^{210} is  where X^9 is N, and X^8 is selected from S, O, and NR^{29}. In some cases, X^8 is NR^{29}. In some cases, R^{29} is H. In some cases, R^{29} is methyl. In some cases, X^8 is O. In some cases, X^8 is S.

[0079] In some embodiments, R^{210} is  where X^{10} is selected from S, O, and NR^{29}. In some cases, X^{10} is O. In some cases, X^{10} is S. In some cases, X^{10} is NR^{29} where R^{29} is $(C_1$-$C_6)$alkyl. In some cases, R^{29} is H. In some cases, R^{29} is methyl.

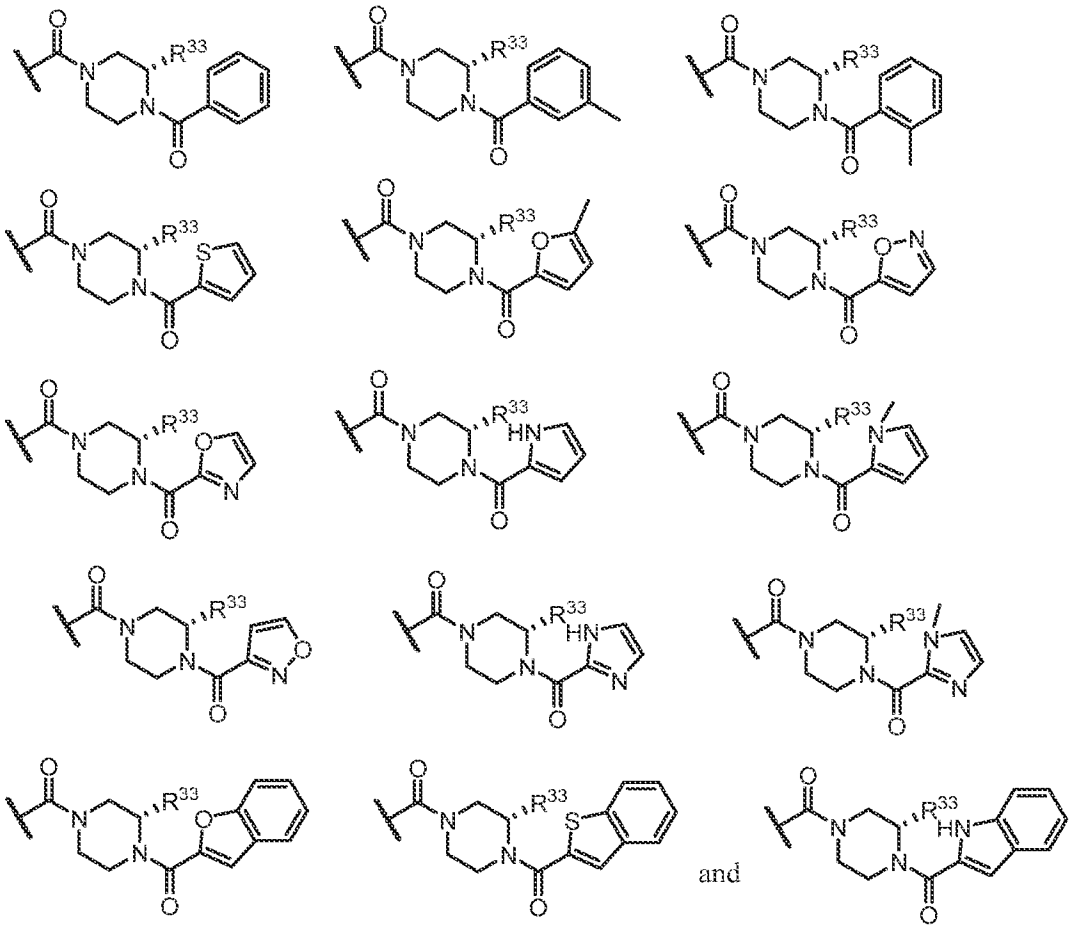
[0080] In some embodiments, R^{210} is  where X^{11} is selected from CH, CR^{31}, S, O, and N, and X^{12} is selected from S, O, and NR^{29}. In some cases, X^{11} is N. In some cases, X^{12} is O or S. In some cases, X^{11} is N, and X^{12} is O. In some cases, X^{11} is N, and X^{12} is S.

[0081] In some embodiments, R^{210} is  where X^{13} is selected from S, O, and NR^{29}. In some cases, X^{13} is NR^{29}. In some cases, R^{29} is H. In some cases, R^{29} is methyl. In some cases, X^{13} is S. In some cases, X^{13} is O.

[0082] In some embodiments of formula (Ia)-(Id), any of R^4-R^{4d} is selected from:



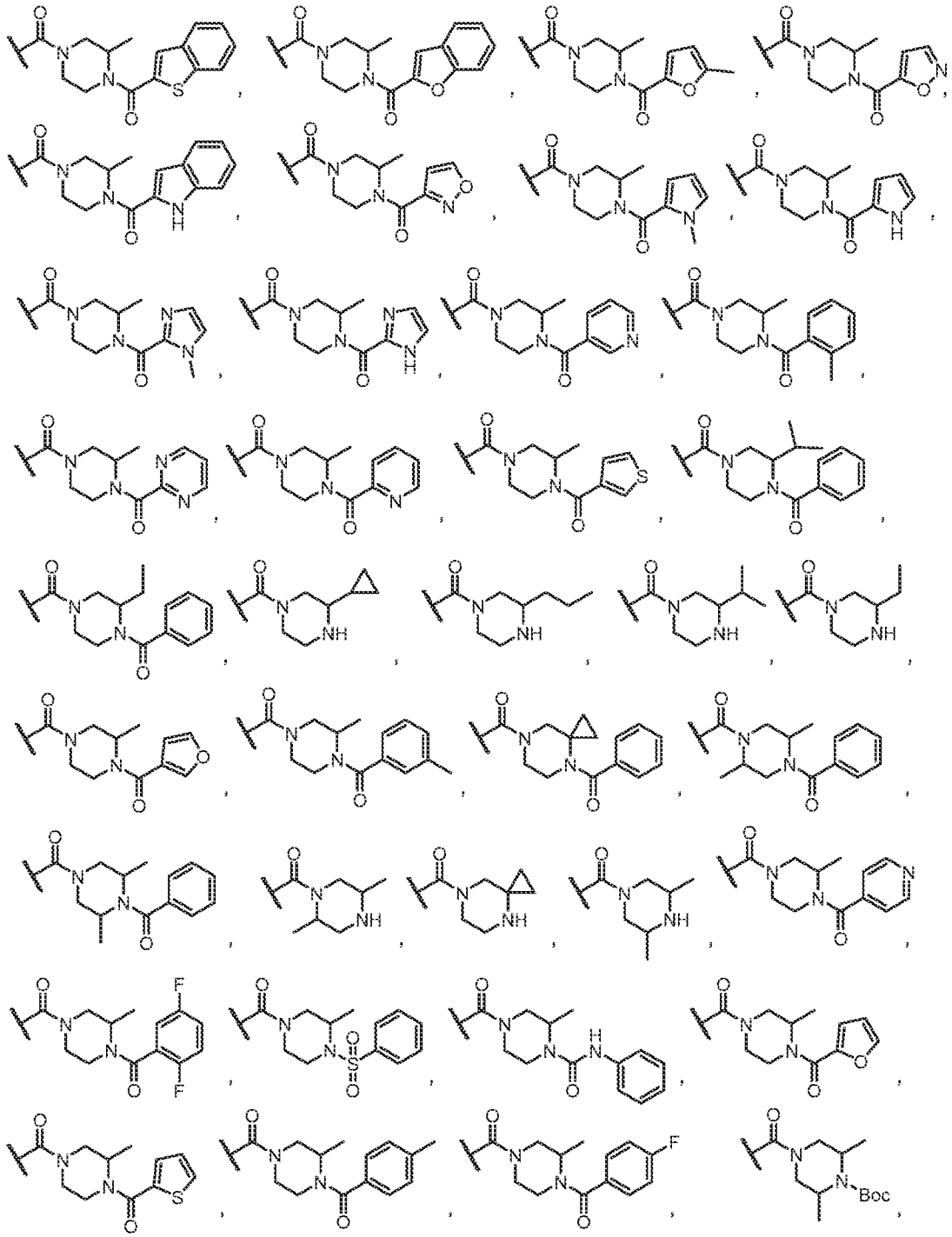
[0083] In some embodiments of formula (Ia)-(Id), any of R^4-R^{4d} is selected from:

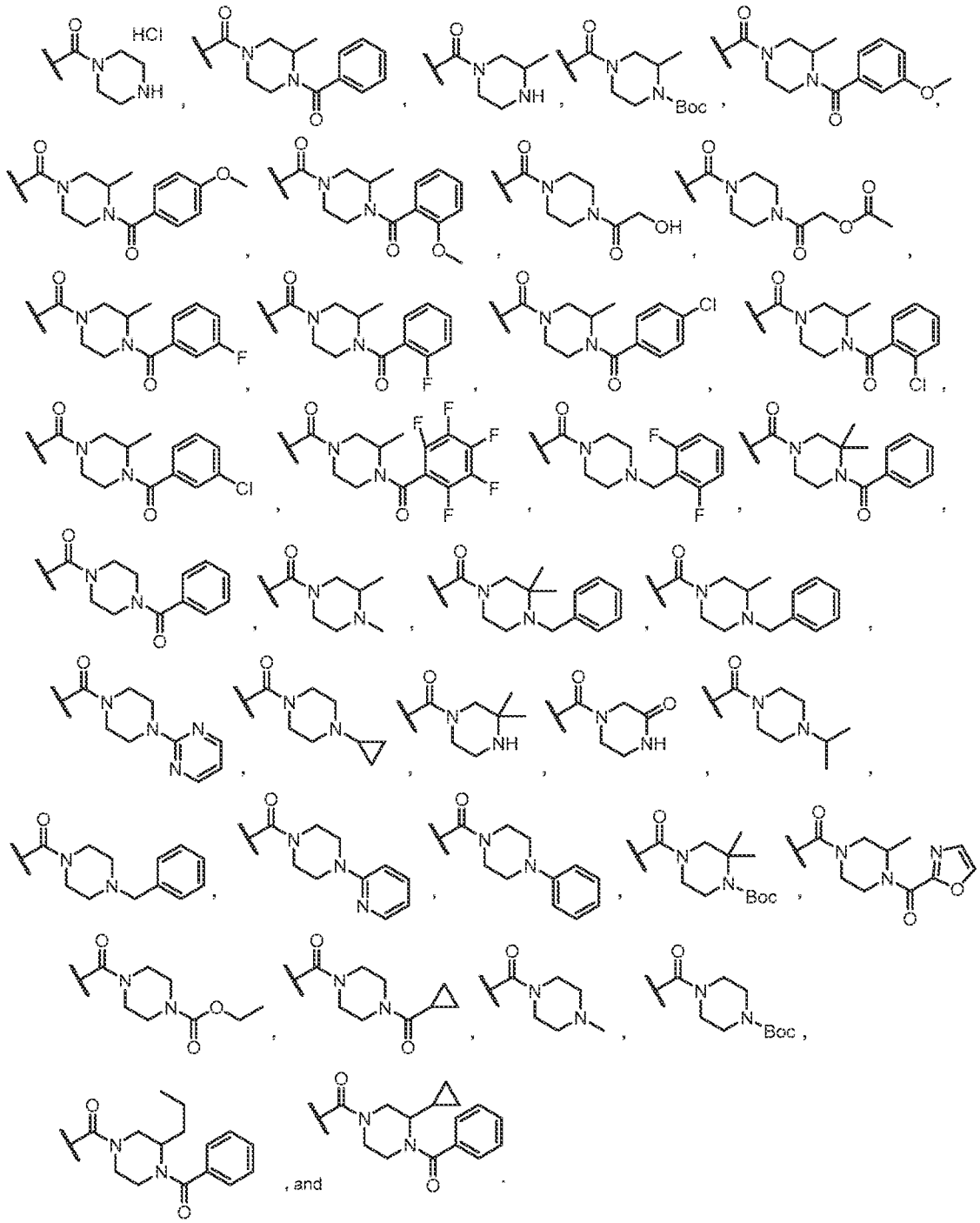


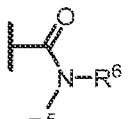
wherein:

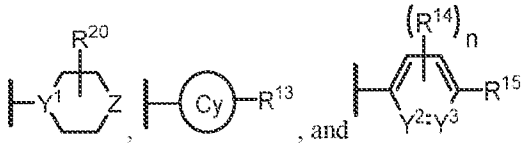
each R^{33} is independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl. In certain cases, each R^{33} is independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases, each R^{33} is methyl. In certain cases, each R^{33} is ethyl. In certain cases, each R^{33} is propyl. In certain cases, each R^{33} is isopropyl. In some embodiments, each R^{33} is independently selected from (C_1-C_6)cycloalkyl. In certain cases, each R^{33} is cyclopropyl. In certain cases, each R^{33} is cyclobutyl. In certain cases, each R^{33} is cyclopentyl. In certain cases, each R^{33} is cyclohexyl.

[0084] In some embodiments of formula (Ia)-(Id), any of R^4-R^{4d} is selected from:





[0085] In some embodiments of formula (Ia)-(Id), any of R^4-R^{4d} is  , R^5 is H or Me, and R^6 is selected from:



; wherein:

Y^1, Y^2, and Y^3 are independently selected from CR^{14} and N;

Z is selected from O, S, CHR^{11}, and NR^{12};

n is 0 to 4;

R^{11} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2a}, $C(O)R^{2b}$, CO_2R^{2c}, $C(O)NR^5R^6$, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, and optionally substituted heterocycle;

R^{12} is selected from H, NH_2, halogen, $C(O)R^{2d}$, CO_2R^{2e}, $C(O)NR^5R^6$, and optionally substituted (C_1-C_5)alkyl;

is selected from optionally substituted (C_1-C_6)alkyl-cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic (C_4-C_{10})carbocycle, and optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle;

R^{13} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2f}, $C(O)R^{2g}$, CO_2R^{2h}, $C(O)NR^5R^6$, NR^5R^6, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, and optionally substituted heterocycle;

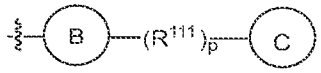
R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle;

R^{15} is selected from H, halogen, $NHC(O)R^{2i}$, OR^{2j}, $C(O)R^{2k}$, $OC(O)R^{2l}$, CO_2R^{2m}, $C(O)NR^5R^6$, NR^5R^6, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, and optionally substituted heterocycle;

R^{20} is selected from H, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted carbocycle, and optionally substituted heterocycle; and

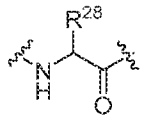
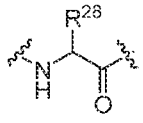
R^{2a}-R^{2m} are independently selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, heterocycle, heteroaryl, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy.

[0086] In some embodiments, R^6 is selected from:



wherein:

ring B and ring C are each independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle;

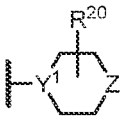
each R^{111} is independently selected from optionally substituted $(C_1$-$C_6)$alkyl,  , -$C(O)(R^{111a})p^1$, -$C(O)O(R^{111b})p^2$, -$S(O)(R^{111c})p^3$, -$SO_2(R^{111d})p^4$, and -$C(O)NR^{27}(R^{111e})p^5$; where R^{111a}-R^{111e} are each independently optionally substituted $(C_1$-$C_6)$alkyl,  ;

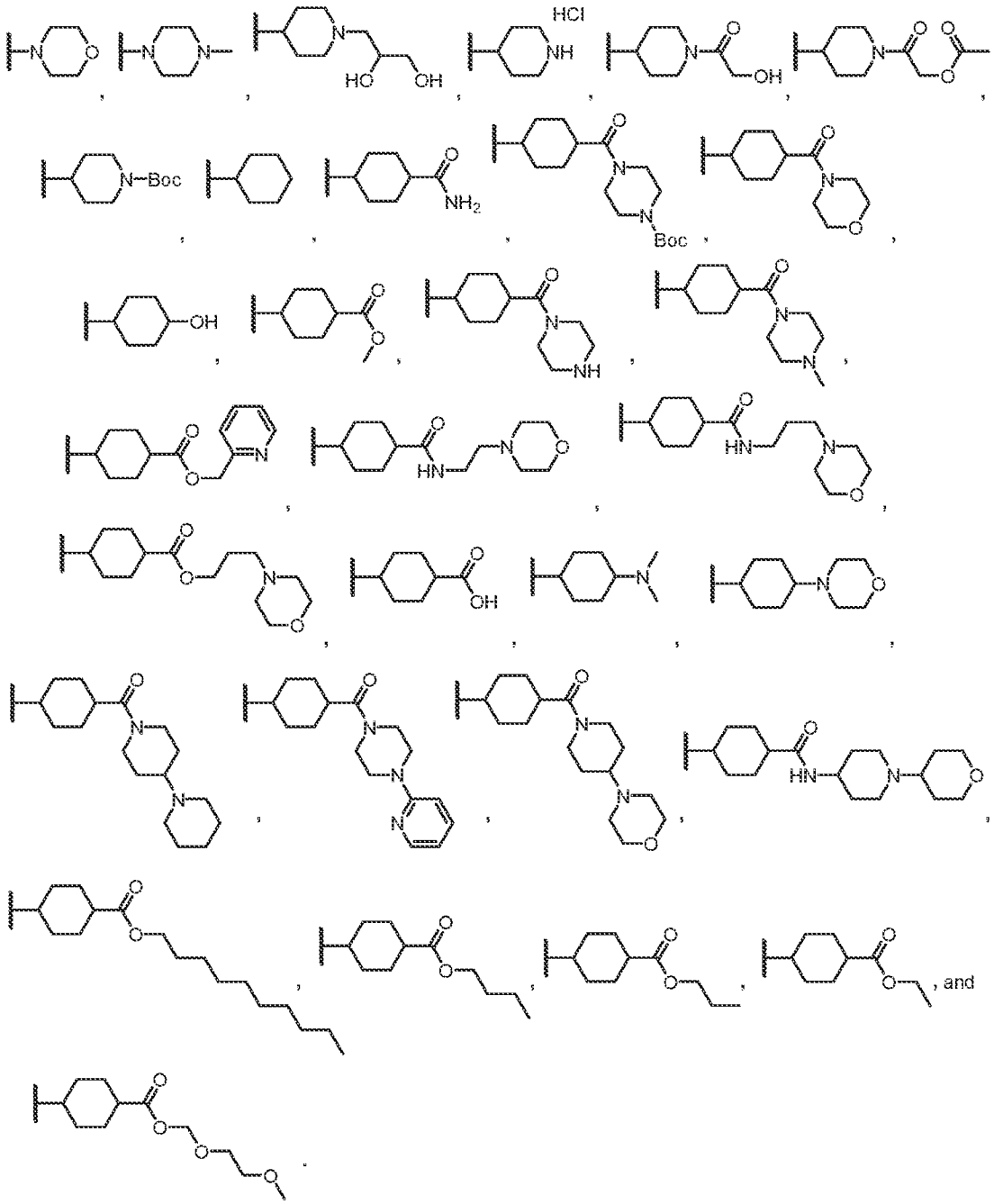
R^{27}-R^{28} are each independently selected from H and optionally substituted $(C_1$-$C_6)$alkyl; and

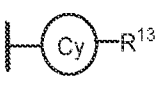
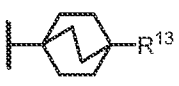
p-p^5 are each independently 0 to 3.

[0087] In some embodiments of R^6, R^{111} is selected from -C(O)-, -C(O)O-, -C(O)NH-, -S(O)-, and -SO_2-; and the B ring and the C ring are independently selected from optionally substituted aryl, optionally substituted carbocycle, optionally substituted heteroaryl and optionally substituted heterocycle. In certain embodiments, R^{111} is -C(O)- and one or both of the B ring and the C ring is optionally substituted aryl. R^{111} is -C(O)O- and one or both of the B ring and the C ring is optionally substituted aryl. R^{111} is -C(O)NH- and one or both of the B ring and the C ring is optionally substituted aryl. R^{111} is -S(O)- and one or both of the B ring and the C ring is optionally substituted aryl. In certain embodiments, R^{111} is -SO_2- and one or both of the B ring and the C ring is optionally substituted aryl. In certain embodiments, R^{111} is -C(O)- and one or both of the B ring and the C ring is optionally substituted carbocycle. R^{111} is -C(O)O- and one or both of the B ring and the C ring is optionally substituted carbocycle. R^{111} is -C(O)NH- and one or both of the B ring and the C ring is optionally substituted carbocycle. R^{111} is -S(O)- and one or both of the B ring and the C ring is optionally substituted carbocycle. In certain embodiments, R^{111} is -SO_2- and one or both of the B ring and the C ring is optionally substituted carbocycle. In certain embodiments, R^{111} is -C(O)- and one or both of the B ring and the C ring is optionally substituted heteroaryl. R^{111} is -C(O)O- and one or both of the B ring and the C ring is optionally substituted heteroaryl. R^{111} is -C(O)NH- and one or both of the B ring and the C ring is optionally substituted heteroaryl. R^{111} is -S(O)- and one or both of the B ring and the C ring is optionally substituted heteroaryl. In certain cases, R^{111} is -SO_2- and one or both of the B ring and the C ring is optionally substituted heteroaryl. In certain embodiments, R^{111} is -C(O)- and one or both of the B ring and the C ring is optionally substituted heterocycle. R^{111} is -C(O)O- and one or both of the B ring and the C ring is optionally substituted heterocycle. R^{111} is -C(O)NH- and one or both of the B ring and the C ring is optionally substituted heterocycle. R^{111} is -S(O)- and one or both of the B ring and the C ring is optionally substituted heterocycle. In certain cases, R^{111} is -SO_2- and one or both of the B ring and the C ring is optionally substituted heterocycle.

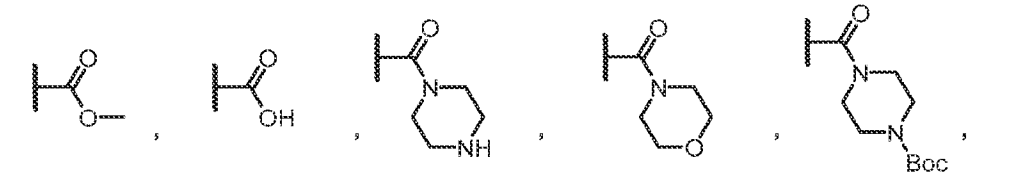
[0088] In certain embodiments, one or both of the B ring and the C ring are optionally substituted piperazine. In certain cases, the B ring is optionally substituted piperazine and the C ring is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle. In certain cases, the C ring is optionally substituted piperazine and the B ring is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle. In certain cases, both the B and the C rings are piperazine.

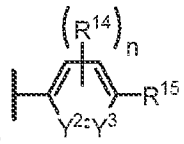
[0089] In some embodiments, R^6 is  and is selected from:



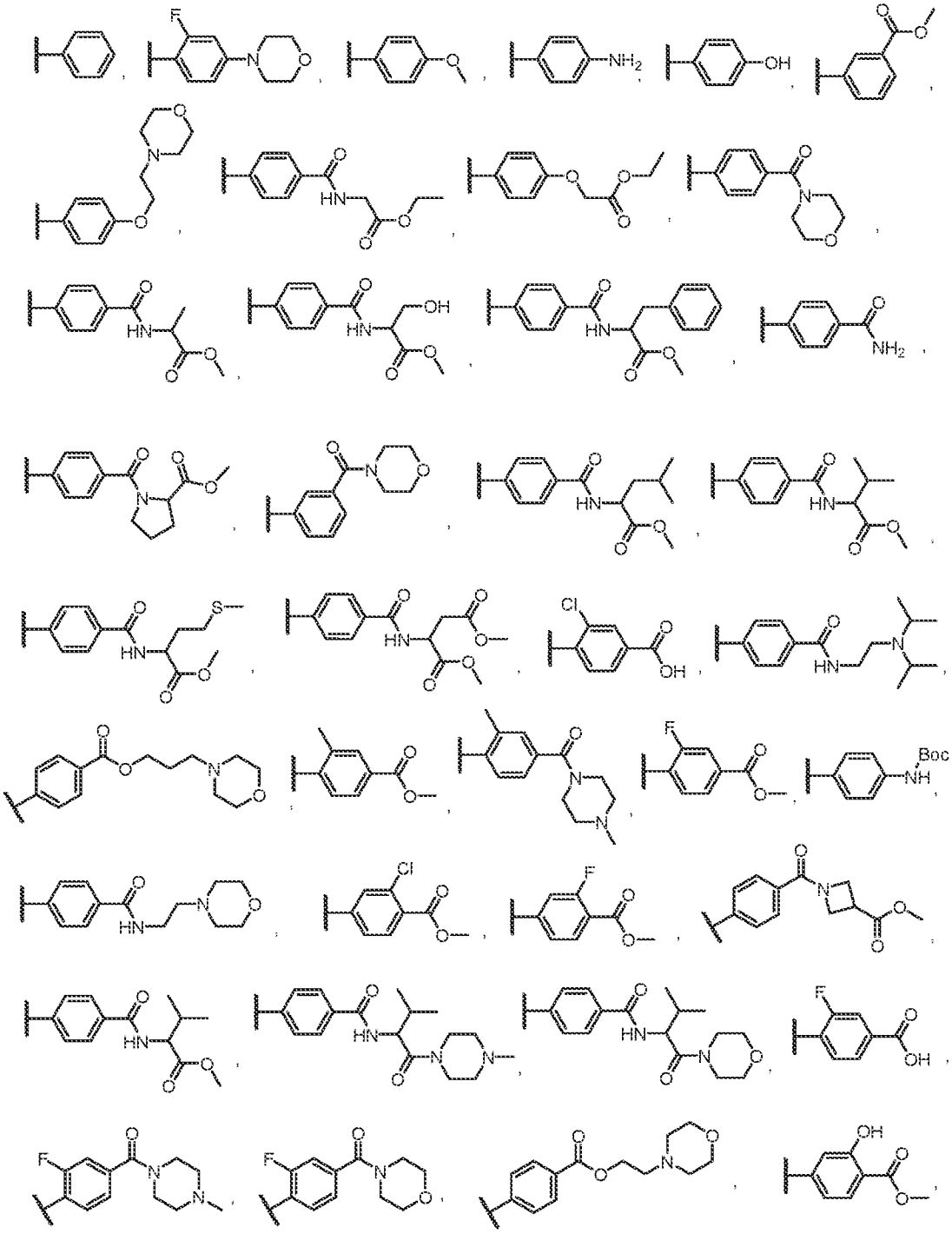
[0090] In some embodiments, R^6 is  and is selected from:  , and  . In certain embodiments, R^{13} is -C(O)OR^{41a}, -NHC(O)R^{41b}, -C(O)NHR^{41c}, C(O)R^{41d}, $C(O)NH_2$, heterocycle, wherein R^{41a}-R^{41d} are independently selected from H, optionally substituted (C_1-C_6)alkyl, optionally substituted heterocycle (e.g., morpholine, piperidine, morpholine-3-one), and optionally substituted (C_1-C_6)alkyl-heterocycle.

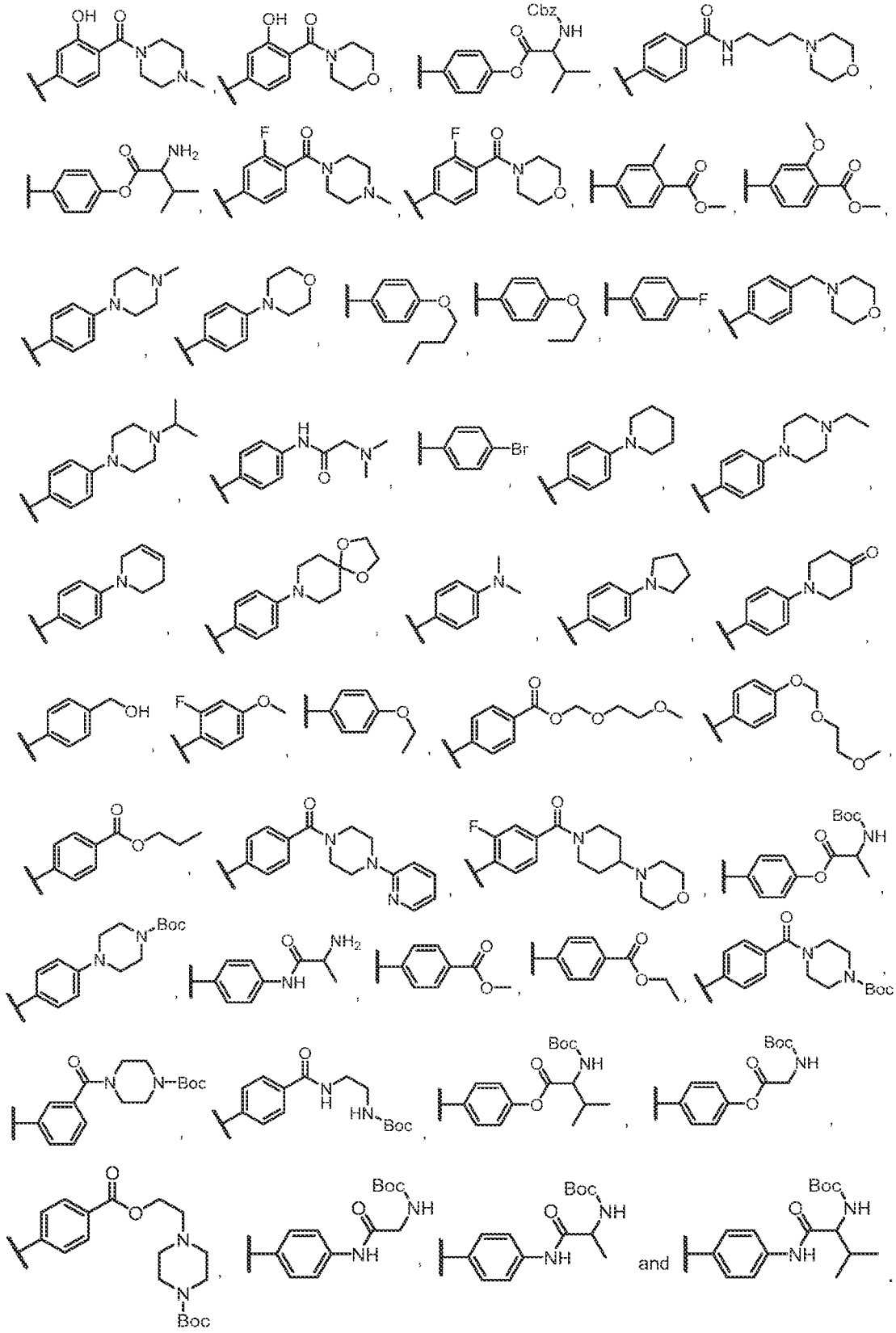
[0091] In some embodiments, R^{13} is selected from:

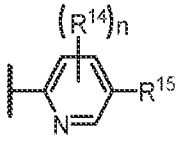


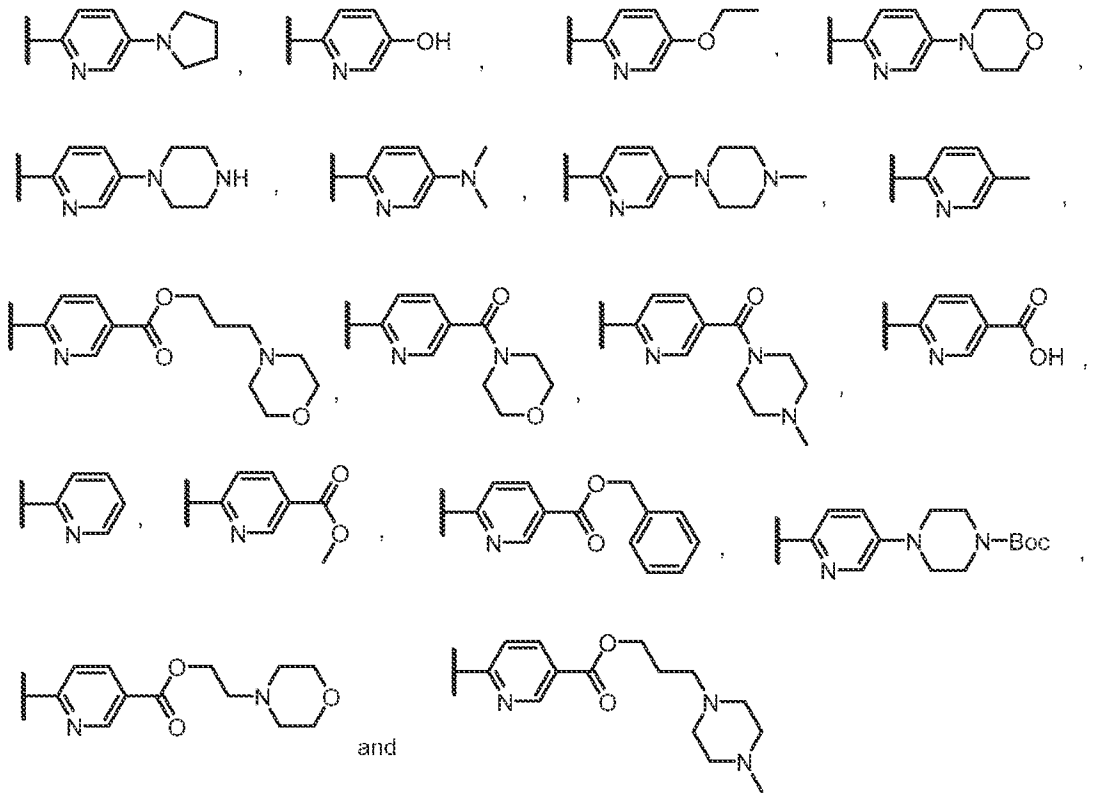
[0092] In some embodiments, R^6 is  . In another embodiment, Y^2 and Y^3 are each CR^{14}. In another embodiment, each R^{14} is independently selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, $-C(O)R^{42f}$, $-OC(O)R^{42g}$, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, wherein R^{42f} to R^{42g} are independently selected from -OH, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted heterocycle (e.g., piperazine, pyrrolidine, azetidine, piperidine, or morpholine), optionally substituted -O-(C_1-C_6)alkyl-heterocycle, and amino acid. In another embodiment, R^{15} is selected from H, halogen,$-OC(O)R^{42a}$, $-C(O)R^{42b}$, $-C(O)NHR^{42c}$, R^{42d} or $-OR^{42e}$, wherein R^{42a} to R^{42e} are independently selected from -OH, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted heterocycle (e.g., piperazine, pyrrolidine, azetidine, piperidine, or morpholine), optionally substituted -O-(C_1-C_6)alkyl-heterocycle, and amino acid. In some embodiments of R^6, where n is 1 or greater, one R^{14} group is $-C(O)R^{42f}$, wherein R^{42f} is selected from optionally substituted heterocycle (e.g., piperazine, pyrrolidine, azetidine, piperidine, or morpholine), and optionally substituted (C_1-C_{10})alkoxy (e.g., $-OCH_3$). In some embodiments of R^6, R^{15} is $-C(O)R^{42b}$, wherein R^{42b} is selected from optionally substituted heterocycle (e.g., piperazine, pyrrolidine, azetidine, piperidine, or morpholine), and optionally substituted (C_1-C_{10})alkoxy (e.g., $-OCH_3$).

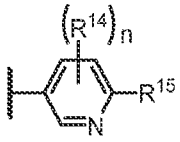
[0093] In some embodiments, R^6 is selected from:

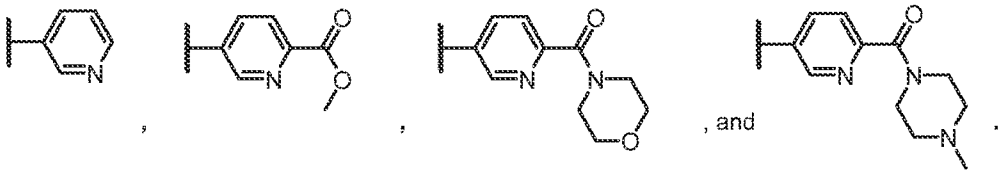




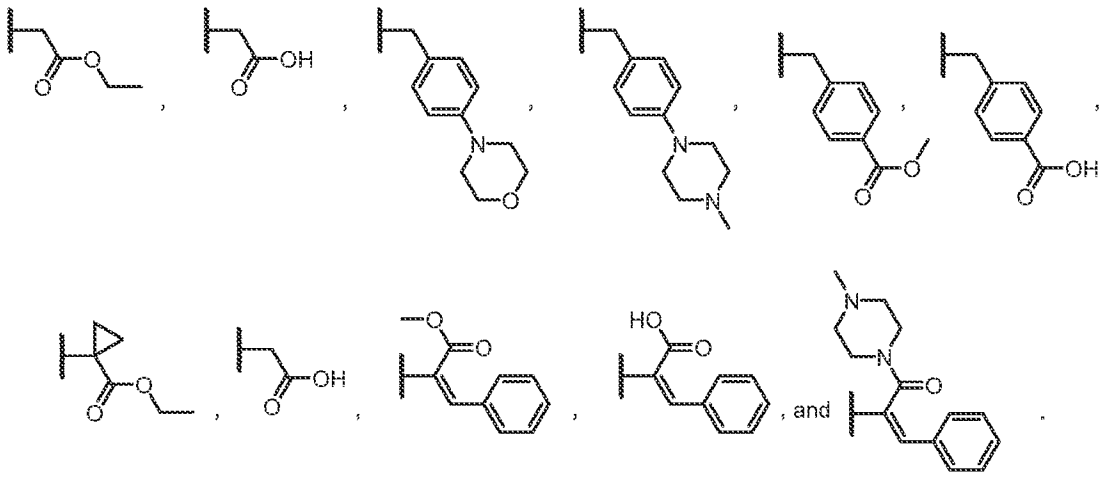
[0094] In some embodiments, R^6 is  and n is 0 to 3. In another embodiment, R^6 is selected from:

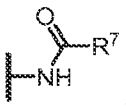


[0095] In some embodiments, R^6 is  and n is 0 to 3. In some embodiments, R^{15} is H, $C(O)OR^{51}$ or $C(O)R^{51}$, where R^{51} is H or optionally substituted (C_1-C_6)alkyl, or optionally substituted heterocycle (e.g., morpholine or piperazine). In another embodiment, R^6 is selected from:



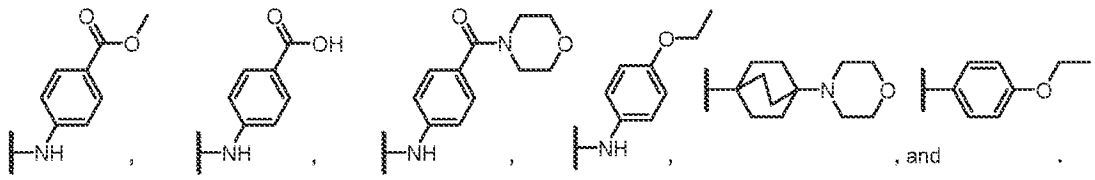
[0096] In some embodiments, R^5 is H or Me, and R^6 is selected from:



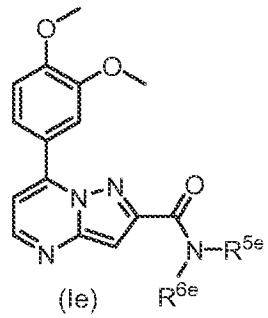
[0097] In some embodiments, R^4 is  .

[0098] In some embodiments, R^7 is selected from optionally substituted N-anilino, optionally substituted phenyl and optionally substituted bicyclic carbocycle.

[0099] In some embodiments, R^7 is selected from:



[00100] In some embodiments, the compound is of formula (Ie):



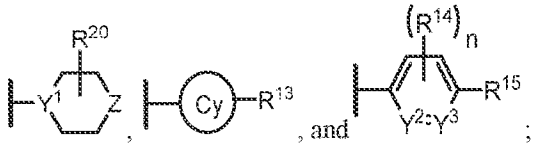
(Ie)

wherein:

R^{5e} and R^{6e} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^{5e} and R^{6e} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle.

[00101] In some embodiments of formula (Ie), R^{5e} is H or Me, and R^{6e} is selected from:



; wherein:

Y^1, Y^2, and Y^3 are independently selected from CR^{14} and N;

Z is selected from O, S, CHR^{11}, and NR^{12};

n is 0 to 4;

R^{11} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2a}, $C(O)R^{2b}$, CO_2R^{2c}, $C(O)NR^5R^6$, optionally substituted amino, optionally substituted $(C_1$-$C_5)$alkyl, and optionally substituted $(C_1$-$C_5)$alkoxy, and optionally substituted heterocycle;

R^{12} is selected from H, NH_2, halogen, $C(O)R^{2d}$, CO_2R^{2e}, $C(O)NR^5R^6$, and optionally substituted $(C_1$-$C_5)$alkyl;

is selected from optionally substituted $(C_1$-$C_6)$alkyl-cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic $(C_4$-$C_{10})$carbocycle, and optionally substituted monocyclic or bicyclic $(C_4$-$C_{10})$heterocycle;

R^{13} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2f}, $C(O)R^{2g}$, CO_2R^{2h}, $C(O)NR^5R^6$, NR^5R^6, optionally substituted $(C_1$-$C_5)$alkyl, and optionally substituted $(C_1$-$C_5)$alkoxy, and optionally substituted heterocycle;

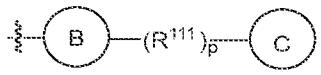
R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted $(C_1$-$C_5)$alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle;

R^{15} is selected from H, halogen, $NHC(O)R^{2i}$, OR^{2j}, $C(O)R^{2k}$, $OC(O)R^{2l}$, CO_2R^{2m}, $C(O)NR^5R^6$, NR^5R^6, optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted $(C_1$-$C_5)$alkoxy, optionally substituted cycloalkyl, and optionally substituted heterocycle; and

R^{20} is selected from H, halogen, optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted $(C_1$-$C_5)$alkoxy, optionally substituted carbocycle, and optionally substituted heterocycle; and

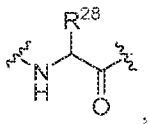
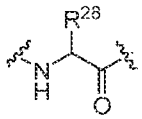
R^{2a}-R^{2m} are independently selected from H, optionally substituted $(C_1$-$C_{10})$ alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, heterocycle, heteroaryl, optionally substituted amino, optionally substituted $(C_1$-$C_5)$alkyl, and optionally substituted $(C_1$-$C_5)$alkoxy.

[00102] In some embodiments, R^{6e} is selected from:



wherein:

ring B and ring C are each independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle;

each R^{111} is independently selected from optionally substituted (C_1-C_6)alkyl,  , -C(O)(R^{111a})p^1, -C(O)O(R^{111b})p^2, -S(O)(R^{111c})p^3, -SO_2(R^{111d})p^4, and -C(O)NR^{27}(R^{111e})p^5; where R^{111a}-R^{111e} are each independently optionally substituted (C_1-C_6)alkyl,  ;

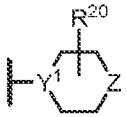
R^{27}-R^{28} are each independently selected from H and optionally substituted (C_1-C_6)alkyl; and

p-p^5 are each independently 0 to 3.

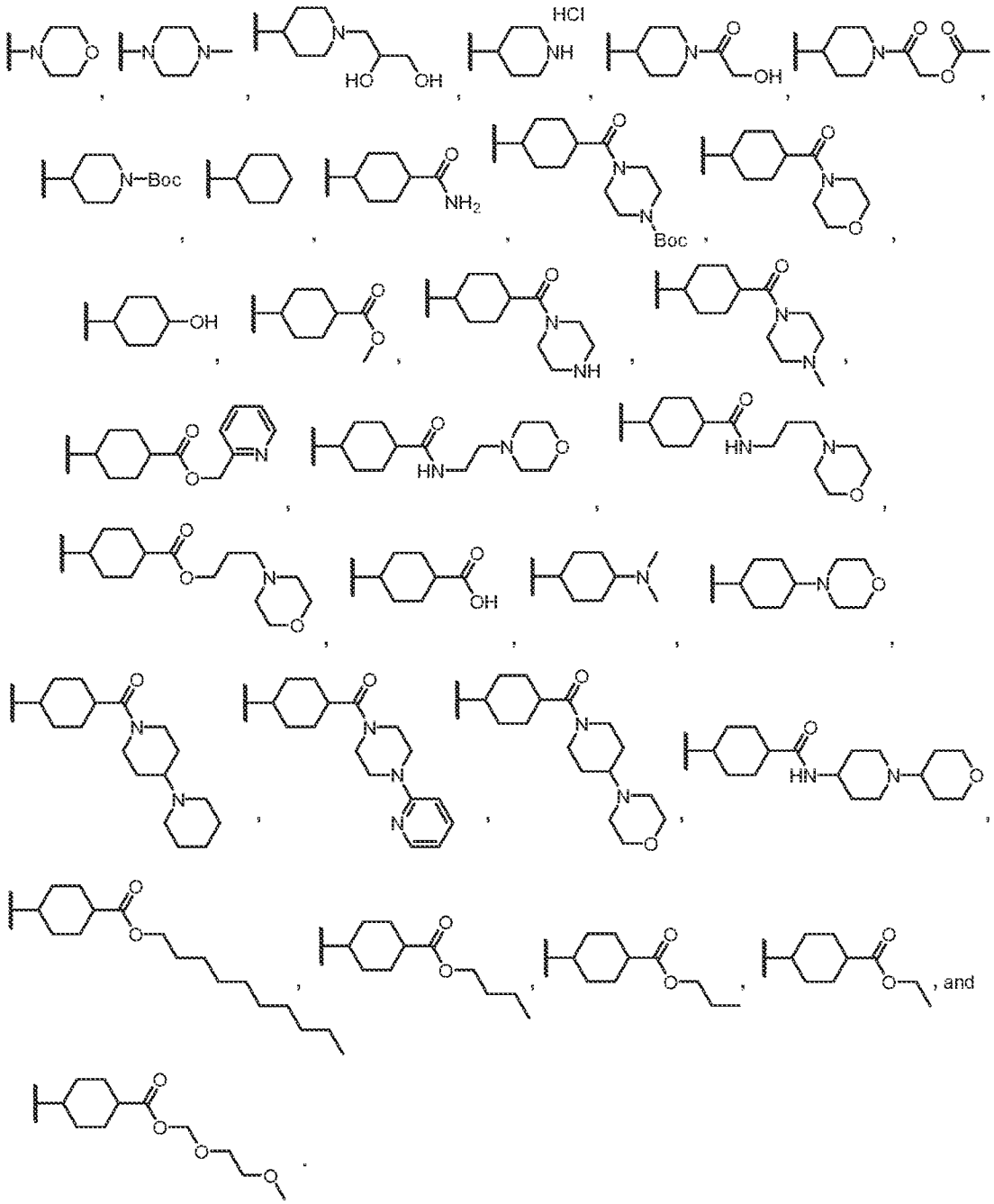
[00103] In some embodiments of R^{6e}, R^{111} is selected from -C(O)-, -C(O)O-, -C(O)NH-, -S(O)- and -SO_2-; and the B ring and the C ring are independently selected from optionally substituted aryl, optionally substituted carbocycle, optionally substituted heteroaryl and optionally substituted heterocycle. In certain embodiments, R^{111} is -C(O)- and one or both of the B ring and the C ring is optionally substituted aryl. In certain embodiments, R^{111} is -C(O)O- and one or both of the B ring and the C ring is optionally substituted aryl. In certain embodiments, R^{111} is -C(O)NH- and one or both of the B ring and the C ring is optionally substituted aryl. In certain embodiments, R^{111} is -S(O)- and one or both of the B ring and the C ring is optionally substituted aryl. In certain embodiments, R^{111} is -SO_2- and one or both of the B ring and the C ring is optionally substituted aryl. In certain embodiments, R^{111} is -C(O)- and one or both of the B ring and the C ring is optionally substituted carbocycle. In certain embodiments, R^{111} is -C(O)O- and one or both of the B ring and the C ring is optionally substituted carbocycle. R^{111} is -C(O)NH- and one or both of the B ring and the C ring is optionally substituted carbocycle. In certain embodiments, R^{111} is -S(O)- and one or both of the B ring and the C ring is optionally substituted carbocycle. In certain embodiments, R^{111} is -SO_2- and one or both of the B ring and the C ring is optionally substituted carbocycle. In certain embodiments, R^{111} is -C(O)- and one or both of the B ring and the C ring is optionally substituted heteroaryl. In certain embodiments, R^{111} is -C(O)O- and one or both of the B ring and the C ring is optionally substituted heteroaryl. In certain embodiments, R^{111} is -C(O)NH- and one or both of the B ring and the C ring is optionally substituted heteroaryl. In certain embodiments, R^{111} is -S(O)- and one or both of the B ring and the C ring is optionally substituted heteroaryl. In certain cases, R^{111} is -SO_2- and one or both of the B ring and the C ring is optionally substituted heteroaryl. In certain embodiments, R^{111} is -C(O)- and one or both of the B ring and the C ring is optionally substituted heterocycle. In certain

embodiments, R^{111} is -C(O)O- and one or both of the B ring and the C ring is optionally substituted heterocycle. In certain embodiments, R^{111} is -C(O)NH- and one or both of the B ring and the C ring is optionally substituted heterocycle. In certain embodiments, R^{111} is -S(O)- and one or both of the B ring and the C ring is optionally substituted heterocycle. In certain cases, R^{111} is $-SO_2-$ and one or both of the B ring and the C ring is optionally substituted heterocycle.

[00104] In certain embodiments, one or both of the B ring and the C ring are optionally substituted piperazine. In certain cases, the B ring is optionally substituted piperazine and the C ring is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle. In certain cases, the C ring is optionally substituted piperazine and the B ring is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle. In certain cases, both the B and the C rings are piperazine.

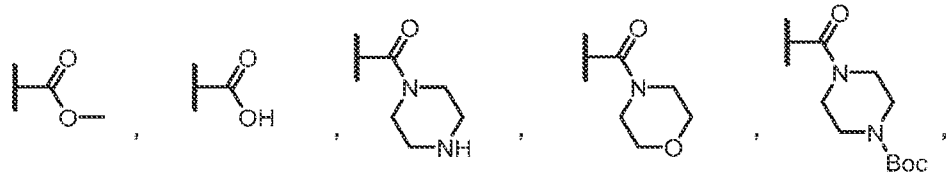
[00105] In some embodiments, R^{6e} is 

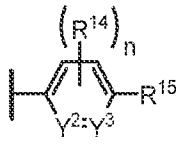
and is selected from:



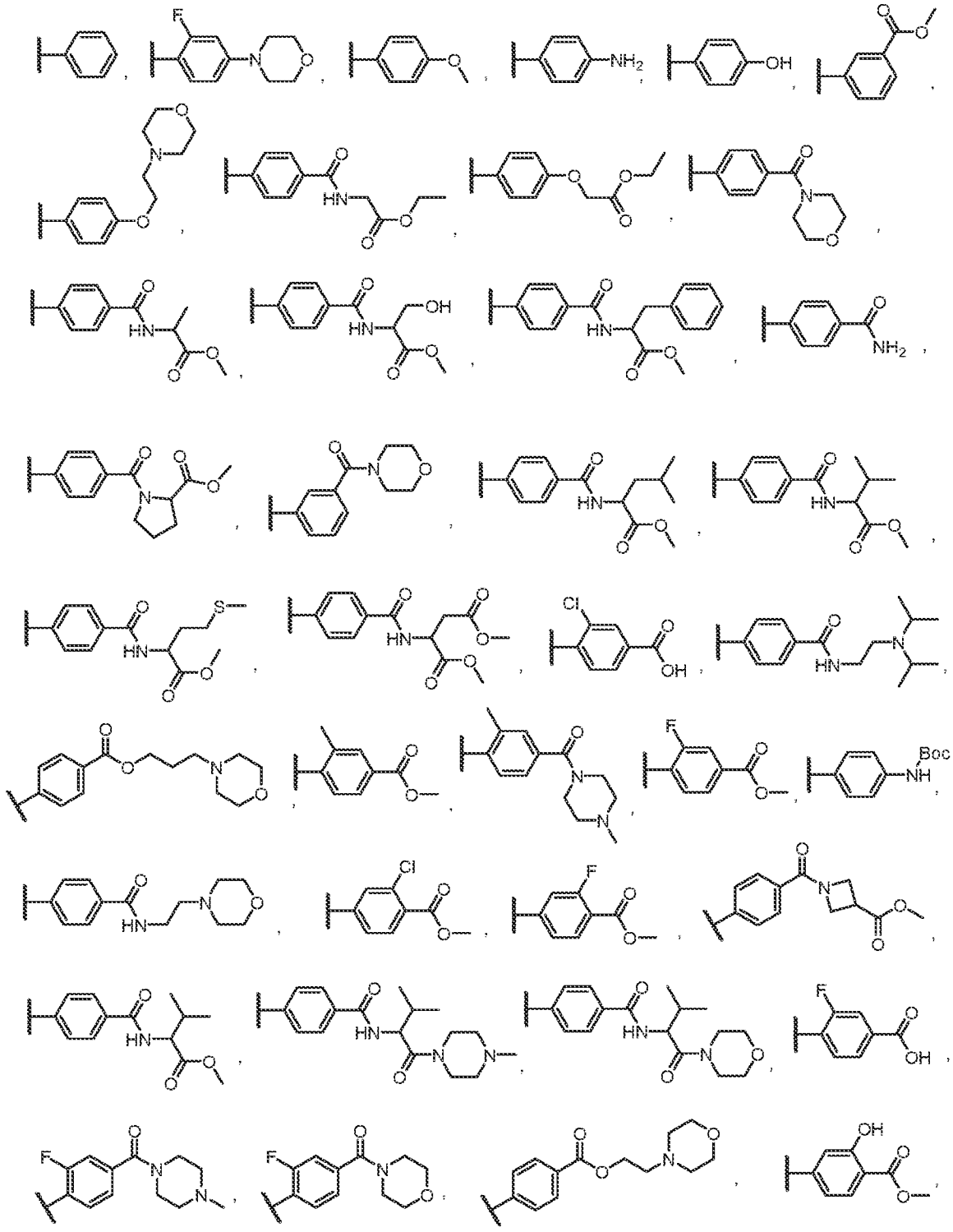
[00106] In some embodiments, R^{6e} is  and is selected from:  , and  . In another embodiment, R^{13} is -C(O)OR^{41a}, -NHC(O)R^{41b}, -C(O)NHR^{41c}, or C(O)R^{41d}, wherein R^{41a}, R^{41b}, R^{41c}, and R^{41d} are independently selected from H, optionally substituted (C_1-C_6)alkyl, optionally substituted heterocycle (e.g., morpholine, piperidine, morpholine-3-one), and optionally substituted (C_1-C_6)alkyl-heterocycle.

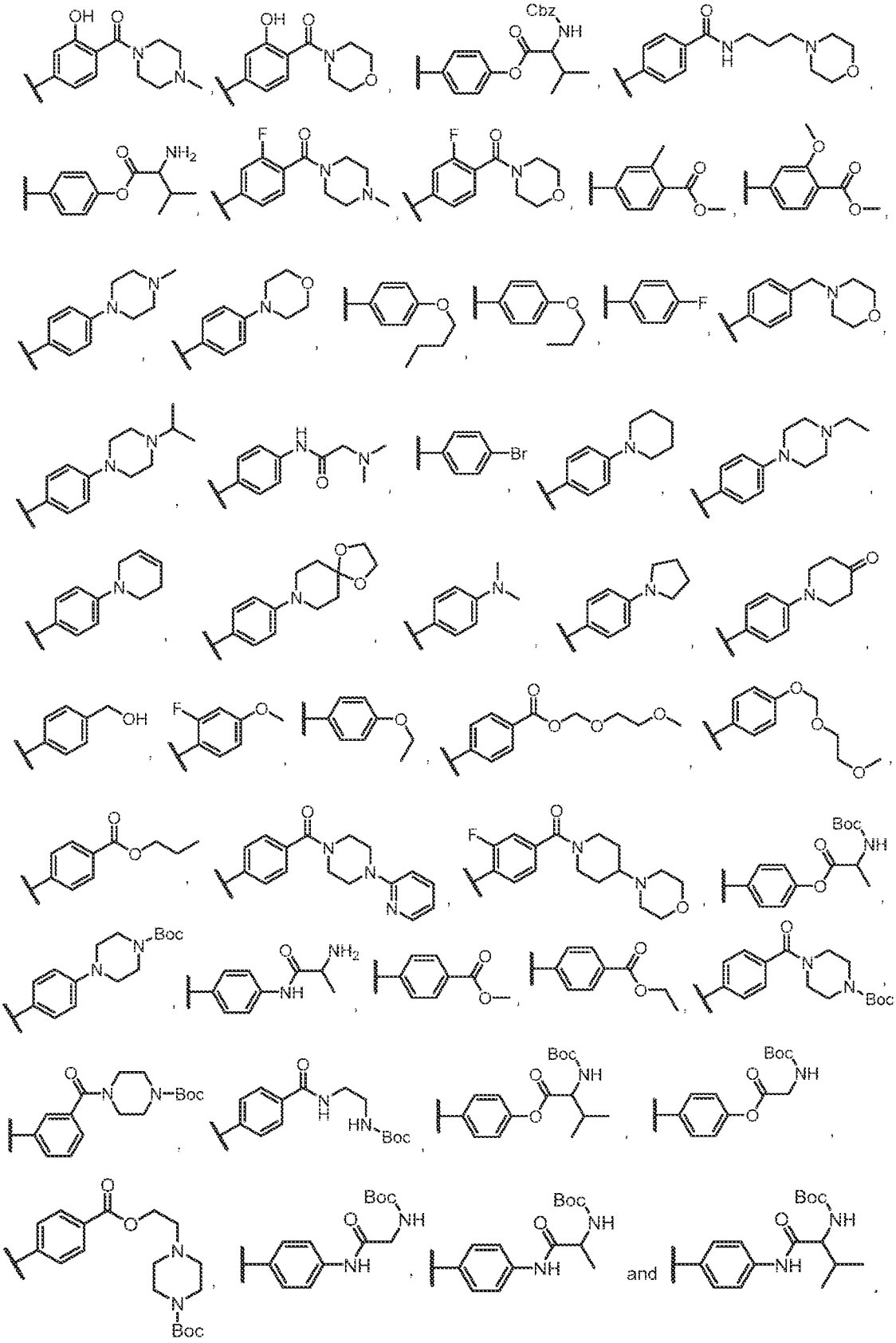
[00107] In some embodiments, R^{13} is selected from:

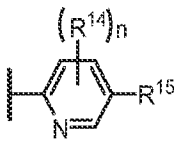


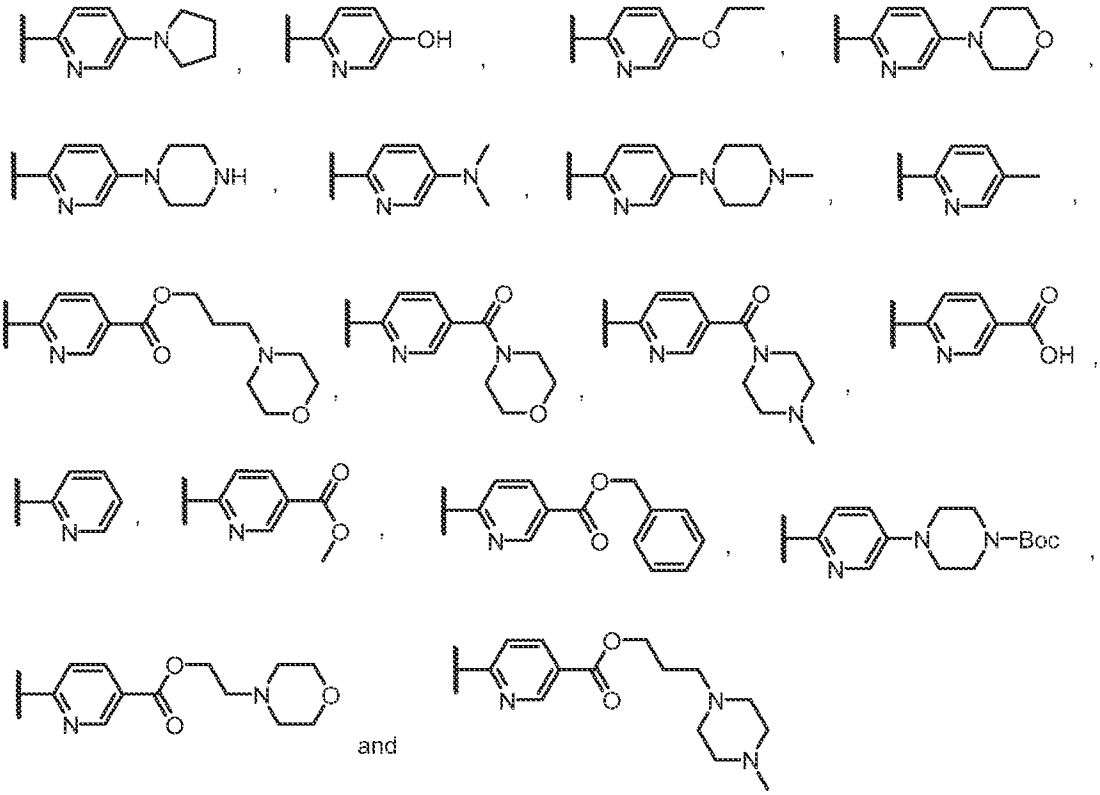
[00108] In some embodiments, R^{6e} is  . In another embodiment, Y^2 and Y^3 are each CR^{14}. In another embodiment, each R^{14} is independently selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, $-C(O)R^{42f}$, $-OC(O)R^{42g}$, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, wherein R^{42f} to R^{42g} are independently selected from -OH, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted heterocycle (e.g., piperidine, or morpholine), optionally substituted $-O-(C_1-C_6)$alkyl-heterocycle, and amino acid. In another embodiment, R^{15} is selected from H, halogen,$-OC(O)R^{42a}$, $-C(O)R^{42b}$, $-C(O)NHR^{42c}$, R^{42d} or $-OR^{42e}$, wherein R^{42a} to R^{42e} are independently selected from -OH, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted heterocycle (e.g., piperidine, or morpholine), optionally substituted $-O-(C_1-C_6)$alkyl-heterocycle, and amino acid. In some embodiments of R^{6e}, where n is 1 or greater, one R^{14} group is $-C(O)R^{42f}$, wherein R^{42f} is selected from optionally substituted heterocycle (e.g., piperidine, or morpholine), and optionally substituted (C_1-C_{10})alkoxy (e.g., $-OCH_3$). In some embodiments of R^{6e}, R^{15} is $-C(O)R^{42b}$, wherein R^{42b} is selected from optionally substituted heterocycle (e.g., piperidine, or morpholine), and optionally substituted (C_1-C_{10})alkoxy (e.g., $-OCH_3$).

[00109] In some embodiments, R^{6e} is selected from:



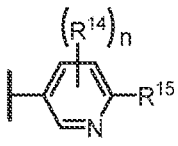


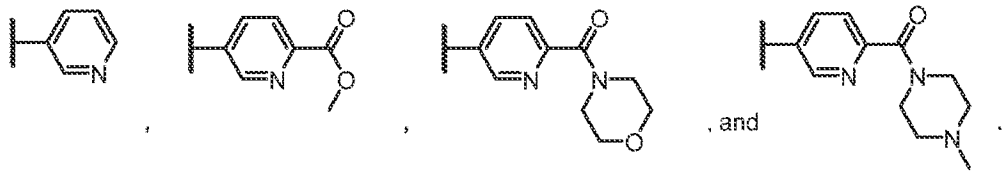
[00110] In some embodiments, R^{6e} is  and n is 0 to 3. In another embodiment, R^{6e} is selected from:



and

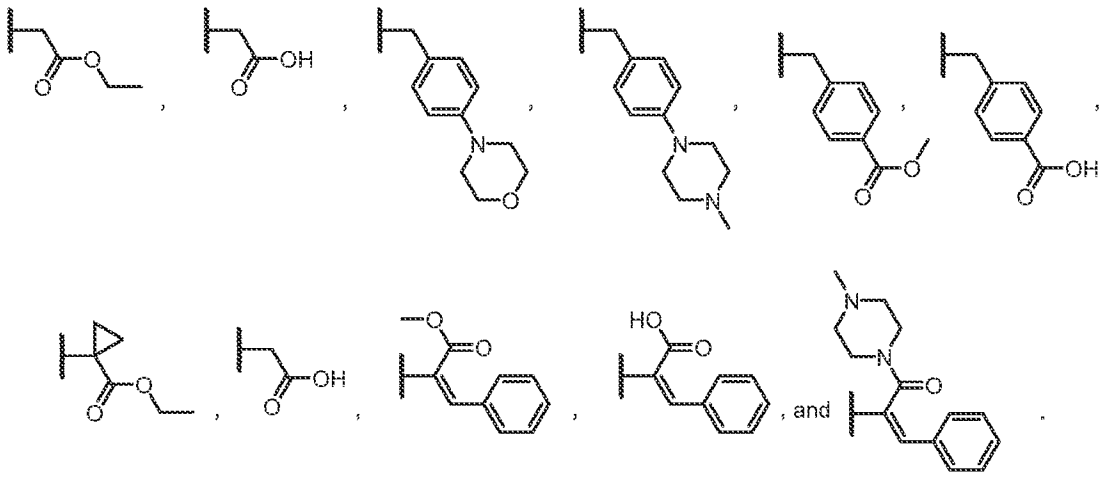
.

[00111] In some embodiments, R^{6e} is  and n is 0 to 3. In some embodiments, R^{15} is H, $-C(O)OR^{51}$ or $-C(O)R^{51}$, where R^{51} is H, optionally substituted (C_1-C_6)alkyl, or optionally substituted heterocycle (e.g., morpholine or piperazine). In another embodiment, R^{6e} is selected from:



, and .

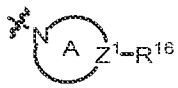
[00112] In some embodiments, R^{5e} is H or Me, and R^{6e} is selected from:



.

[00113] In some embodiments of formula (Ie), R^{5e} and R^{6e} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle.

[00114] In some embodiments of formula (Ie) R^{5e} and R^{6e} together with the nitrogen atom to which they are attached are cyclically linked to form:



wherein:

ring A is an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle;

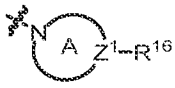
Z^1 is CR^{14} or N, where R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle; and

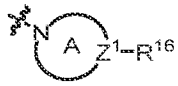
R^{16} is selected from H, halogen, $-OR^{22a}$, $-C(O)R^{22b}$, $-CO_2R^{22c}$, and $-C(O)NR^{50}R^{60}$, $-NR^{50}R^{60}$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

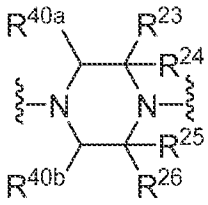
R^{22a}, R^{22b}, and R^{22c} are independently selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

R^{50} and R^{60} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^{50} and R^{60} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted heterocycle, or an optionally substituted heteroaryl.

[00115] In some embodiments of formula (Ie) when R^{5e} and R^{6e} together form:  and the A ring is piperidine, then R^{16} comprises at least one cyclic group selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle. In some cases, the A ring is piperidine and R^{16} comprises an optionally substituted aryl. In some cases, the optionally substituted aryl is optionally substituted phenyl. In some cases, the A ring is piperidine and R^{16} comprises an optionally substituted heteroaryl. In some cases, the A ring is piperidine and R^{16} comprises an optionally substituted carbocycle. In some cases, the A ring is piperidine and R^{16} comprises an optionally substituted heterocycle.

[00116] In some embodiments of formula (Ie) when R^{5e} and R^{6e} together form:  , the A ring is an optionally substituted piperazine, pyrrolidine, or azetidine. In certain cases, the A ring is:



wherein:

R^{23}-R^{26} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; or

one or both of R^{23}-R^{24} and R^{25}-R^{26} together with the carbon atom to which they are attached are cyclically linked to form an optionally substituted carbocycle or an optionally substituted heterocycle; and

R^{40a} and R^{40b} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle.

[00117] In some embodiments of the A ring, R^{23} is selected from optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl; and R^{24}-R^{26}, R^{40a} and R^{40b} are each H. In certain cases, R^{23} is selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases, R^{23} is methyl. In

certain cases, R^{23} is ethyl. In certain cases, R^{23} is propyl. In certain cases, R^{23} is isopropyl. In some embodiments, R^{23} is (C_1-C_6)cycloalkyl. In certain cases, R^{23} is cyclopropyl. In certain cases, R^{23} is cyclobutyl. In certain cases, R^{23} is cyclopentyl. In certain cases, R^{23} is cyclohexyl.

[00118] In certain embodiments of the A ring, two of R^{23}, R^{25}, and R^{40b} are independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and the other one of R^{23}, R^{25} and R^{40b} is H, and R^{24}, R^{26} and R^{40a} are each H. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are optionally substituted (C_1-C_6)alkyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are each independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are methyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are ethyl. In certain cases, two of R^{23}, R^{25}, and R^{40b} are propyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are isopropyl. In some embodiments of the A ring, two of R^{23}, R^{25}, and R^{40b} are (C_1-C_6)cycloalkyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are cyclopropyl. In certain cases, two of R^{23}, R^{25}, and R^{40b} are cyclobutyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are cyclopentyl. In certain cases of the A ring, two of R^{23}, R^{25}, and R^{40b} are cyclohexyl.

[00119] In certain embodiments of the A ring, R^{23} and R^{25} are each independently selected from optionally substituted (C_1-C_6)alkyl, and optionally substituted cycloalkyl; and R^{24}, R^{26} and R^{40a}-R^{40b} are each H. In certain cases of the A ring, both R^{23} and R^{25} are optionally substituted (C_1-C_6)alkyl. In certain cases of the A ring, R^{23} and R^{25} are each independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases of the A ring, both R^{23} and R^{25} are methyl. In certain cases of the A ring, both R^{23} and R^{25} are ethyl. In certain cases of the A ring, both R^{23} and R^{25} are propyl. In certain cases of the A ring, both R^{23} and R^{25} are isopropyl. In some embodiments of the A ring, both R^{23} and R^{25} are (C_1-C_6)cycloalkyl. In certain cases of the A ring, both R^{23} and R^{25} are cyclopropyl. In certain cases, both R^{23} and R^{25} are cyclobutyl. In certain cases of the A ring, both R^{23} and R^{25} are cyclopentyl. In certain cases of the A ring, both R^{23} and R^{25} are cyclohexyl.

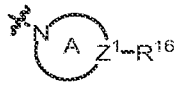
[00120] In certain embodiments of the A ring, R^{23} and R^{40b} are each independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and R^{24}-R^{26} and R^{40a} are each H. In certain cases, both R^{23} and R^{40b} are optionally substituted (C_1-C_6)alkyl. In certain cases, R^{23} and R^{40b} are each independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases, both R^{23} and R^{40b} are methyl. In certain cases, both R^{23} and R^{40b} are ethyl. In certain cases, both R^{23} and R^{40b} are propyl. In certain cases, both R^{23} and R^{40b} are isopropyl. In some embodiments, both R^{23} and R^{40b} are (C_1-C_6)cycloalkyl. In certain cases, both R^{23} and R^{40b} are cyclopropyl. In certain cases, both R^{23} and R^{40b} are cyclobutyl. In certain cases, both R^{23} and R^{40b} are cyclopentyl. In certain cases, both R^{23} and R^{40b} are cyclohexyl.

[00121] In certain embodiments of the A ring, R^{23} and R^{24} are each independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and R^{25}-R^{26}, R^{40a} and

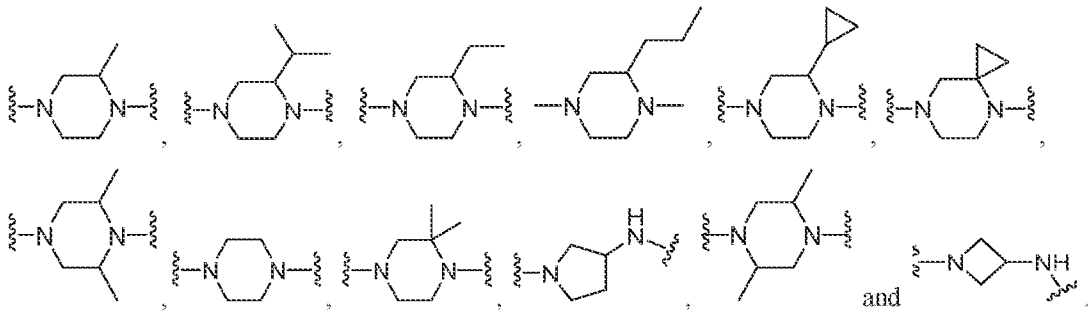
R^{40b} are each H. In certain cases, both R^{23} and R^{24} are optionally substituted (C_1-C_6)alkyl. In certain cases, R^{23} and R^{24} are each independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases, both R^{23} and R^{24} are methyl. In certain cases, both R^{23} and R^{24} are ethyl. In certain cases, both R^{23} and R^{24} are propyl. In certain cases, both R^{23} and R^{25} are isopropyl. In some embodiments, both R^{23} and R^{24} are (C_1-C_6)cycloalkyl. In certain cases, both R^{23} and R^{24} are cyclopropyl. In certain cases, both R^{23} and R^{24} are cyclobutyl. In certain cases, both R^{23} and R^{24} are cyclopentyl. In certain cases, both R^{23} and R^{24} are cyclohexyl.

[00122] In certain embodiments of the A ring, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a carbocycle; and R^{25}-R^{26}, R^{40a} and R^{40b} are each H. In some embodiments, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a (C_1-C_6)cycloalkyl. In certain cases, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a cyclopropyl. In certain cases, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a cyclobutyl. In certain cases, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a cyclopentyl. In certain cases, R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a cyclohexyl.

[00123] In some embodiments of formula (Ie) when R^{5e} and R^{6e} together form:

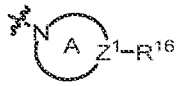


, the A ring is selected from:

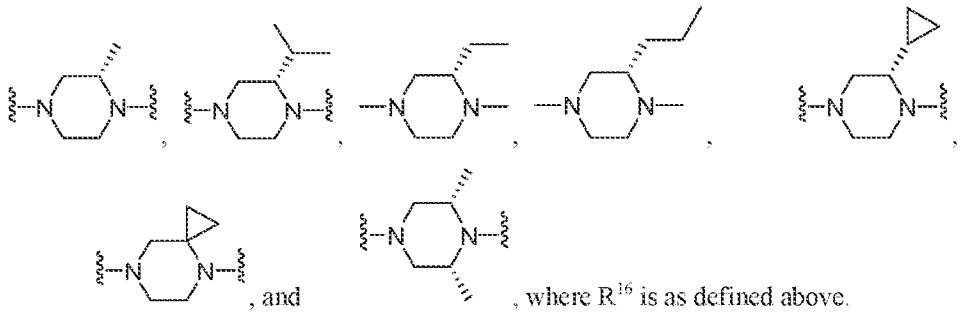


In some embodiments, R^{16} is selected from H, halogen, $-OR^{22a}$, $-C(O)R^{22b}$, $-CO_2R^{22c}$, and $-C(O)NR^{50}R^{60}$, $-NR^{50}R^{60}$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, where R^{22a}, R^{22b}, R^{22c}, R^{50}, and R^{60} are as defined above.

[00124] In some embodiments of formula (Ie) when R^{5e} and R^{6e} together form:

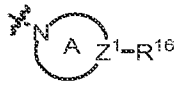


, the A ring is selected from:



, where R^{16} is as defined above.

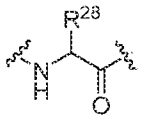
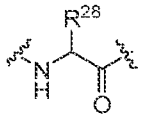
[00125] In some embodiments of formula (Ie), R^{5e} and R^{6e} together form:



, wherein R^{16} is:

$$-(R^{110})_nR^{210}$$

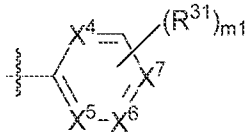
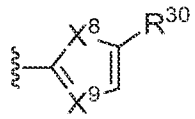
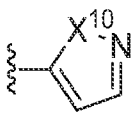
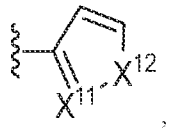
wherein:

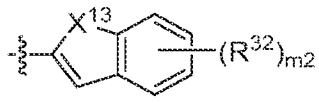
each R^{110} is independently selected from optionally substituted (C_1-C_6)alkyl,  , -C(O)(R^{110a})n^1, -C(O)O(R^{110b})n^2, -S(O)(R^{110c})n^3, -SO_2(R^{110d})n^4, and -C(O)NR^{27}(R^{110e})n^5; where R^{110a}-R^{110e} are each independently optionally substituted (C_1-C_6)alkyl,  ; R^{27}-R^{28} are each independently selected from H and optionally substituted (C_1-C_6)alkyl; and n-n^5 are each independently 0 to 3; and

R^{210} is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle.

[00126] In some embodiments, R^{110} is selected from -C(O)-, -C(O)O-, -C(O)NH-, -S(O)-, and -SO_2-; and R^{210} is selected from optionally substituted aryl and optionally substituted heteroaryl. In certain embodiments, R^{110} is -C(O)- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -C(O)O- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -C(O)NH- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -S(O)- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -SO_2- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -C(O)- and R^{210} is optionally substituted aryl. In certain embodiments, R^{110} is -C(O)O- and R^{210} is optionally substituted heteroaryl. In certain embodiments, R^{110} is -C(O)NH- and R^{210} is optionally substituted heteroaryl. In certain embodiments, R^{110} is -S(O)- and R^{210} is optionally substituted heteroaryl. In certain cases, R^{110} is -SO_2- and R^{210} is optionally substituted heteroaryl.

[00127] In some embodiments, R^{210} is selected from:





, and


,wherein:

wherein:

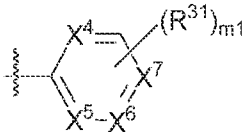
X^4-X^7, X^9, and X^{11} are each independently selected from CH, CR^{31}, S, O, and N;

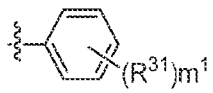
X^8, X^{10}, X^{12} and X^{13} are each independently selected from S, O, and NR^{29};

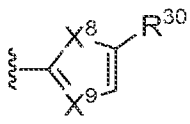
R^{29} is selected from H and optionally substituted (C_1-C_6)alkyl;

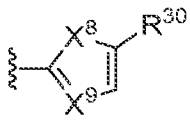
R^{30}-R^{32} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

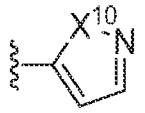
m^1-m^2 are each independently 0 to 5.

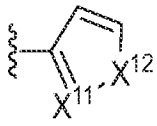
[00128] In some embodiments, R^{210} is  , where X^4-X^7 are each independently selected from CH, CR^{31}, S, O, and N. In some embodiments, R^{210} is

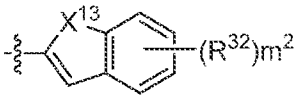

.

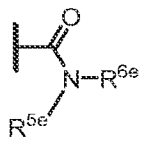
[00129] In some embodiments, R^{210} is  where X^9 is selected from CH, CR^{31}, S, O, and N; and X^8 is selected from S, O, and NR^{29}. In some cases, R^{29} is methyl. In some embodiments of R^{210} is X^9 is CH, CR^{31}, S, O, and N; and X^8 is selected from S, O, and NR^{29}. In some cases, X^9 is CH, and X^8 is S. In some cases, R^{30} is H. In some cases, R^{30} is methyl. In some embodiments, X^9 is CH, X^8 is S, and R^{30} is H. In some cases, X^9 is CH, X^8 is NR^{29}, and R^{30} is H. In some cases, X^9 is CH, and X^8 is NH. In some cases, X^9 is CH, X^8 is O and R^{30} is (C_1-C_6)alkyl. In some cases, X^9 is CH, X^8 is O and R^{30} is methyl.

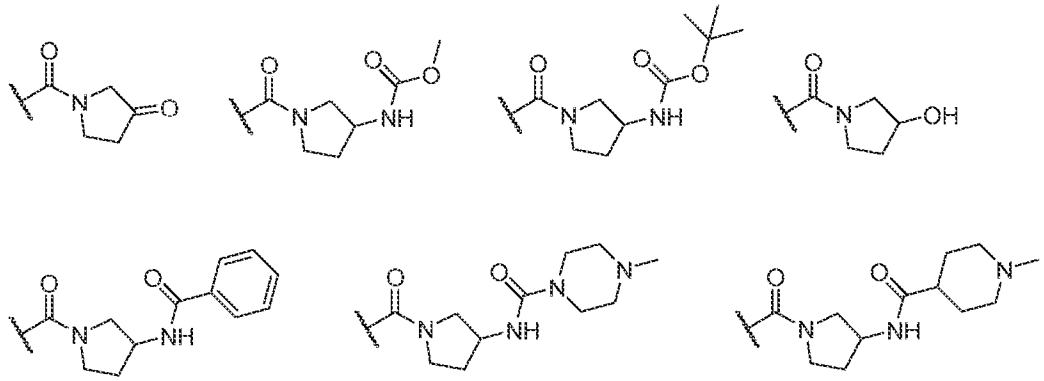
[00130] In some embodiments, R^{210} is  where X^9 is N, and X^8 is selected from S, O, and NR^{29}. In some cases, X^8 is NR^{29}. In some cases, R^{29} is H. In some cases, R^{29} is methyl. In some cases, X^8 is O. In some cases, X^8 is S.

[00131] In some embodiments, R^{210} is  where X^{10} is selected from S, O, and NR^{29}. In some cases, X^{10} is O. In some cases, X^{10} is S. In some cases, X^{10} is NR^{29} where R^{29} is (C_1-C_6)alkyl. In some cases, R^{29} is H. In some cases, R^{29} is methyl.

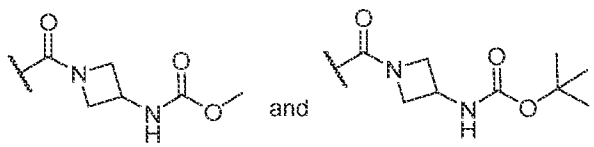
[00132] In some embodiments, R^{210} is  where X^{11} is selected from CH, CR^{31}, S, O, and N, and X^{12} is selected from S, O, and NR^{29}. In some cases, X^{11} is N. In some cases, X^{12} is O or S. In some cases, X^{11} is N, and X^{12} is O. In some cases, X^{11} is N, and X^{12} is S.

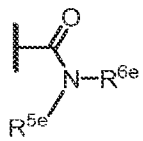
[00133] In some embodiments, R^{210} is  where X^{13} is selected from S, O, and NR^{29}. In some cases, X^{13} is NR^{29}. In some cases, R^{29} is H. In some cases, R^{29} is methyl. In some cases, X^{13} is S. In some cases, X^{13} is O.

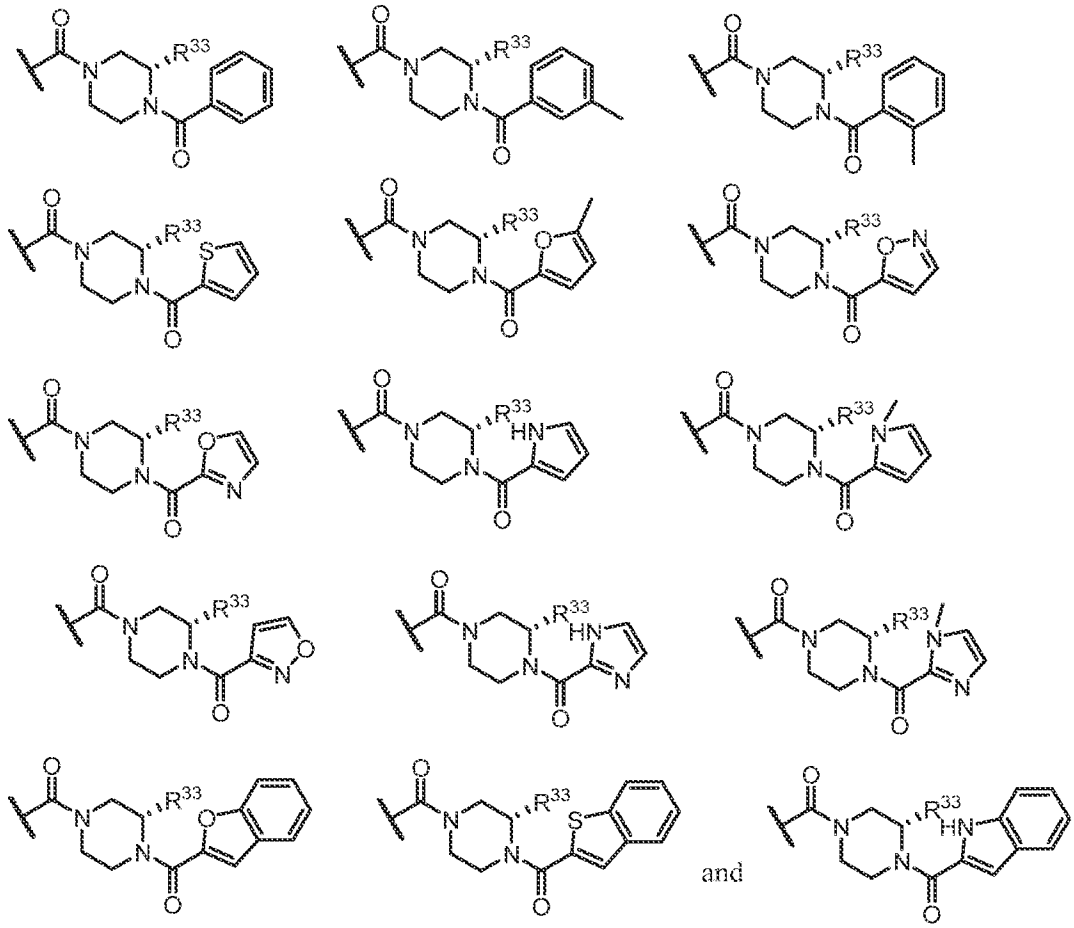
[00134] In some embodiments of formula (Ie),  is selected from:



and



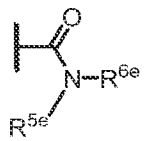
[00135] In some embodiments of formula (Ie),  is selected from:

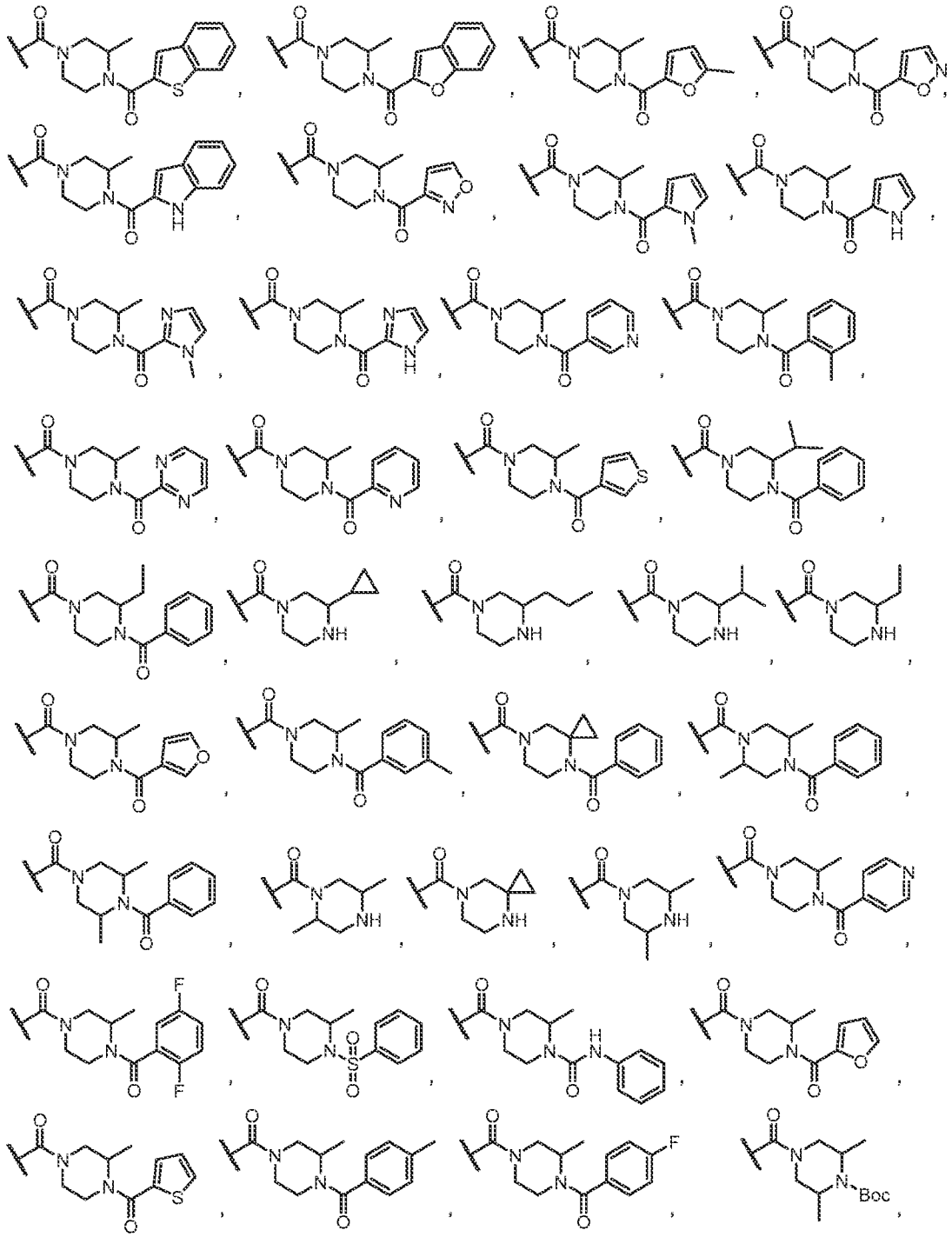


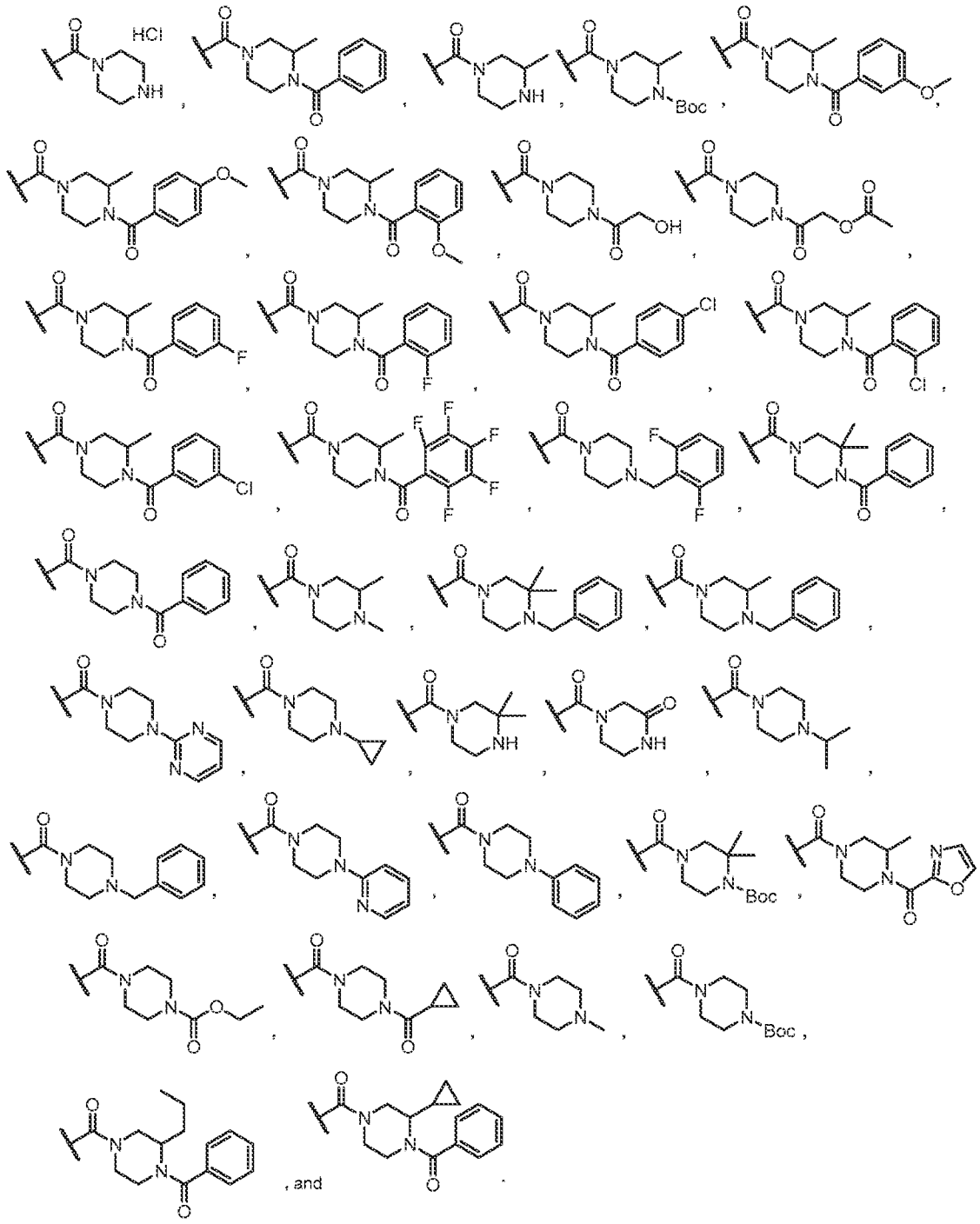
,

wherein:

each R^{33} is independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl. In certain cases, each R^{33} is independently selected from methyl, ethyl, propyl, isopropyl, butyl, and t-butyl. In certain cases, each R^{33} is methyl. In certain cases, each R^{33} is ethyl. In certain cases, each R^{33} is propyl. In certain cases, each R^{33} is isopropyl. In some embodiments, each R^{33} is independently selected from (C_1-C_6)cycloalkyl. In certain cases, each R^{33} is cyclopropyl. In certain cases, each R^{33} is cyclobutyl. In certain cases, each R^{33} is cyclopentyl. In certain cases, each R^{33} is cyclohexyl.

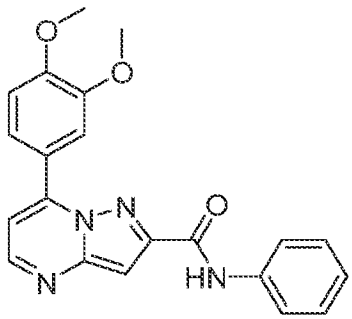
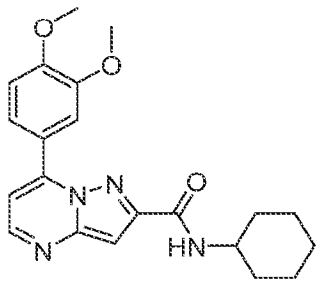
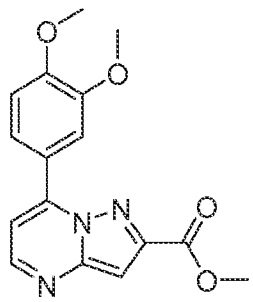
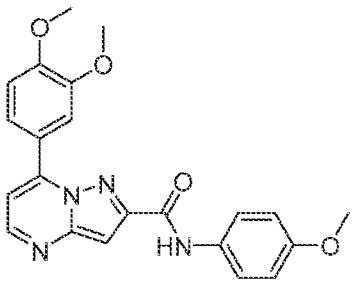
[00136] In some embodiments of formula (Ie),  is selected from:

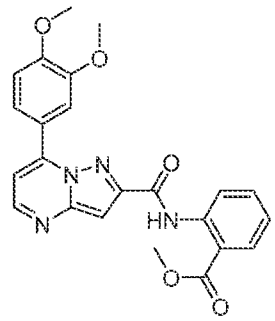
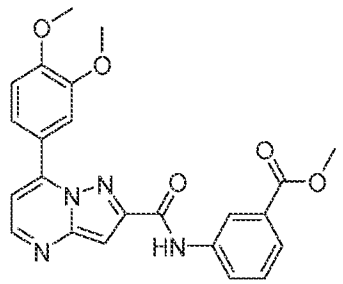
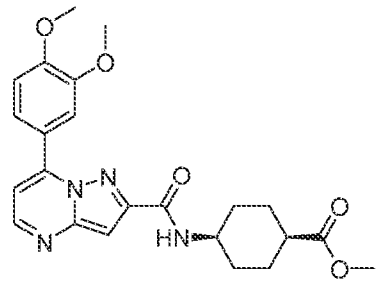
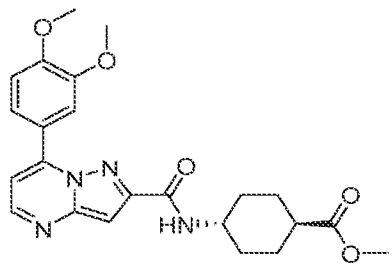
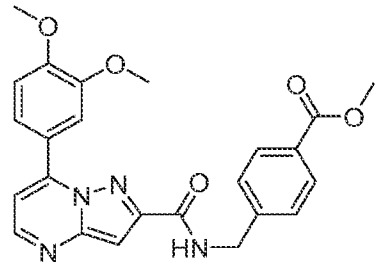


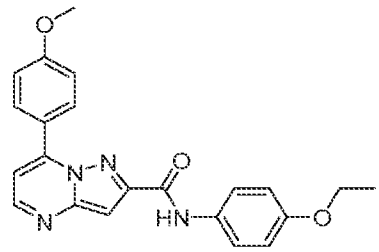
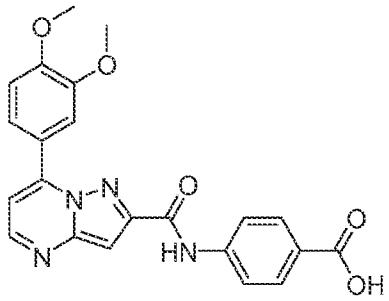
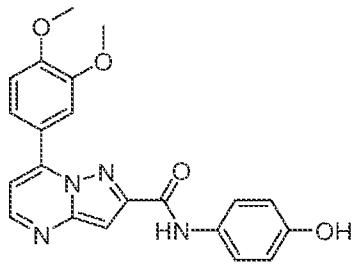
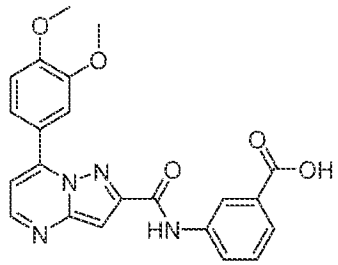
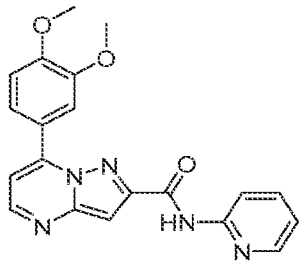


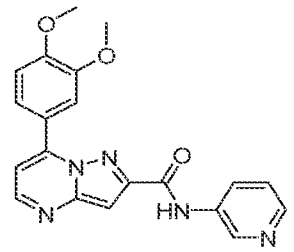
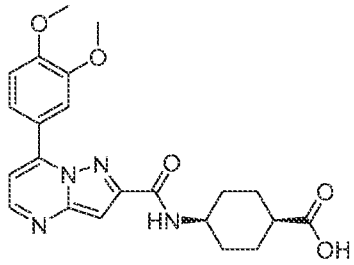
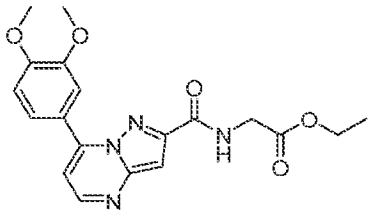
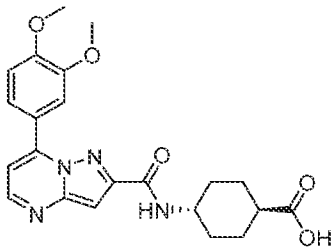
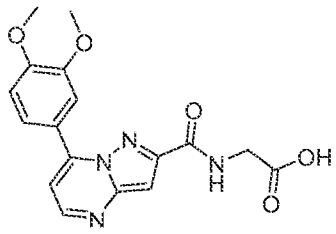
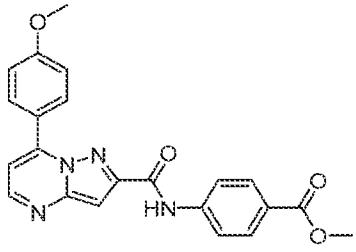
[00137] In some embodiments of formula (Ia)-(Ie), the compound is of Table 1, or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof.

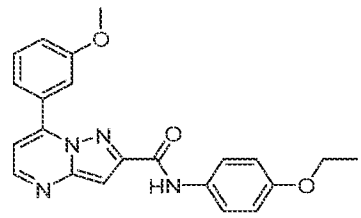
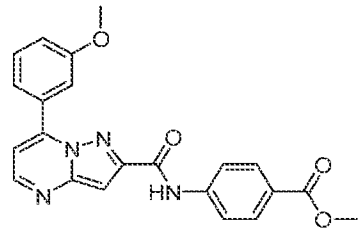
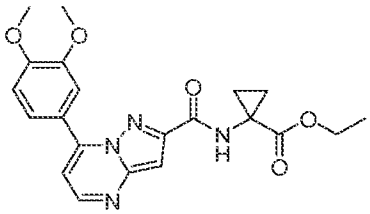
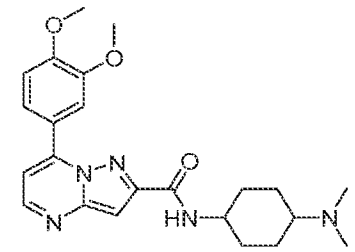
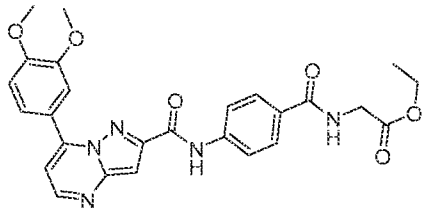
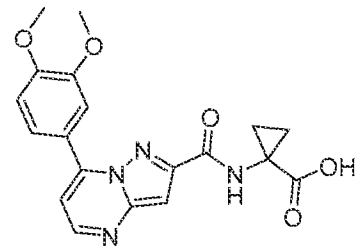
Table 1: Exemplary compounds

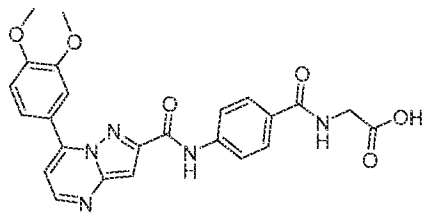
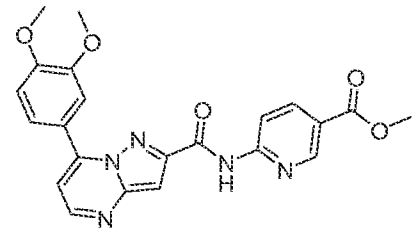
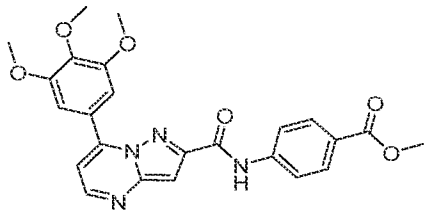
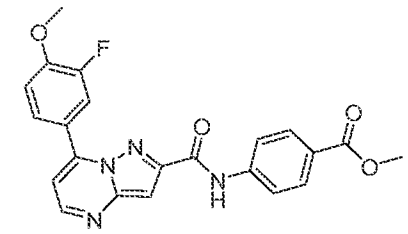
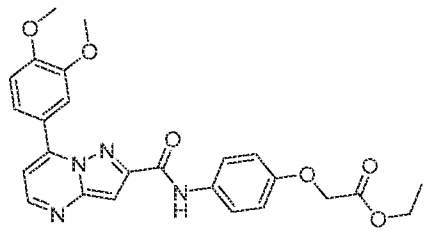
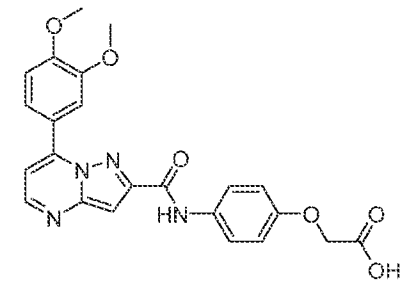
Cmpd	Structure	Name
1		7-(3,4-dimethoxyphenyl)-N-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
2		N-cyclohexyl-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
4		methyl 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate
6		7-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

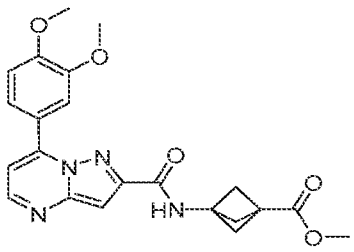
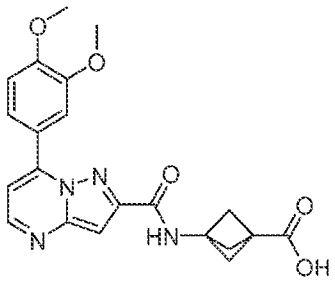
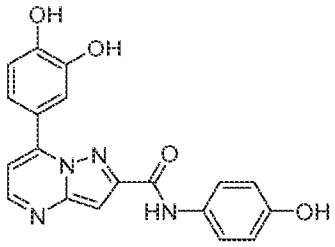
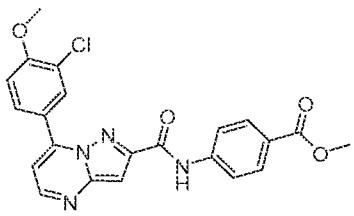
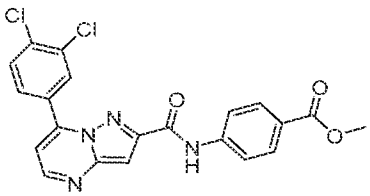
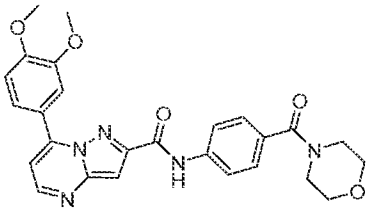
7		methyl 2-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
8		methyl 3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
9		methyl (1S,4S)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
10		methyl (1r,4r)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
12		methyl 4-((7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)methyl)benzoate

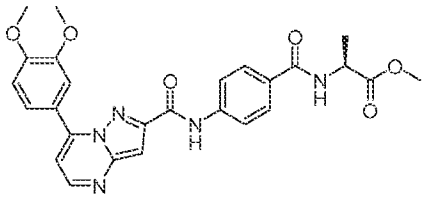
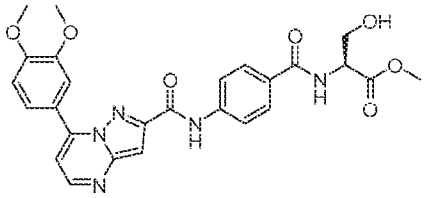
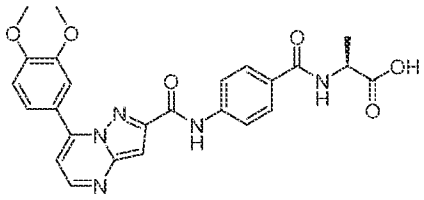
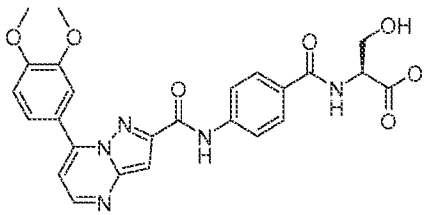
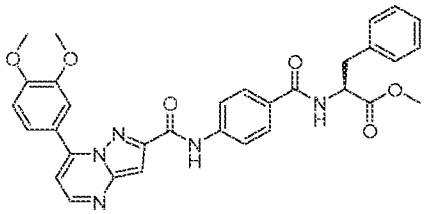
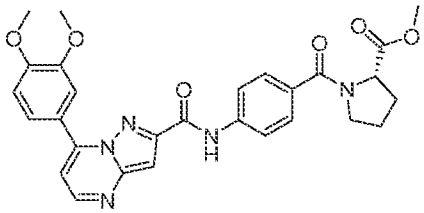
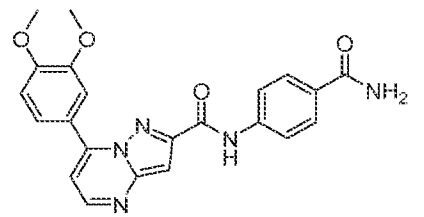
13		N-(4-ethoxyphenyl)-7-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
14		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoic acid
15		7-(3,4-dimethoxyphenyl)-N-(4-hydroxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
16		3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoic acid
17		7-(3,4-dimethoxyphenyl)-N-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

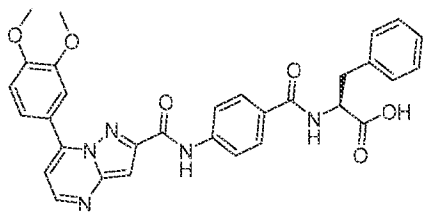
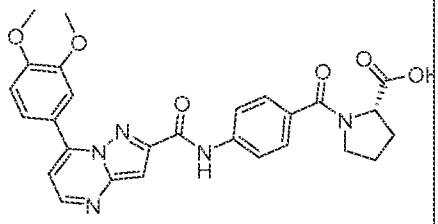
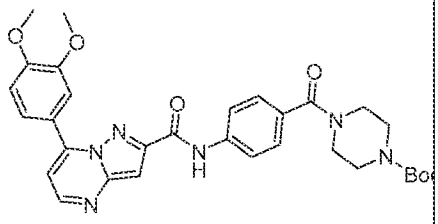
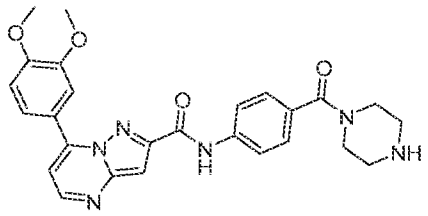
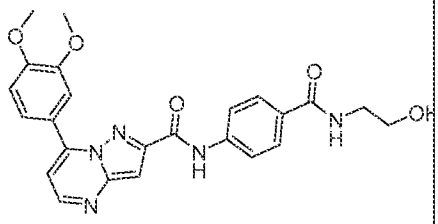
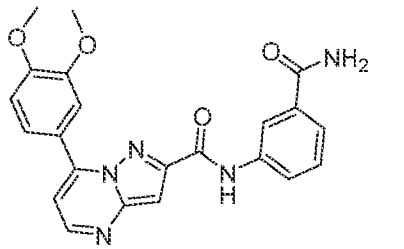
18		7-(3,4-dimethoxyphenyl)-N-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
19		(1S,4S)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylic acid
20		ethyl (7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)glycinate
21		(1R,4R)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylic acid
22		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)glycine
23		methyl 4-(7-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate

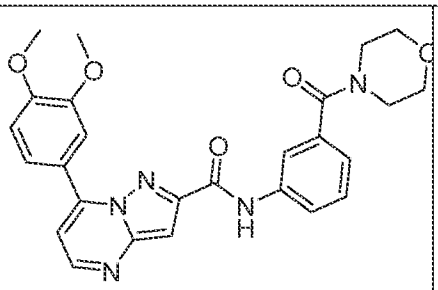
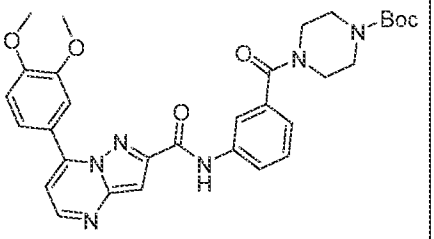
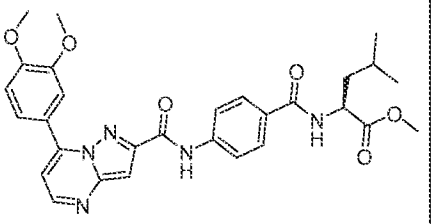
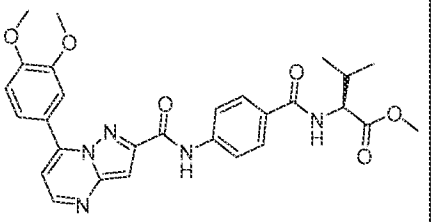
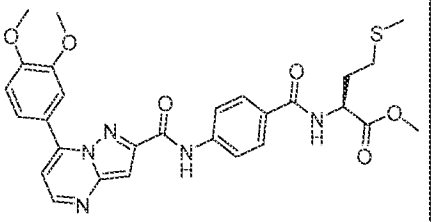
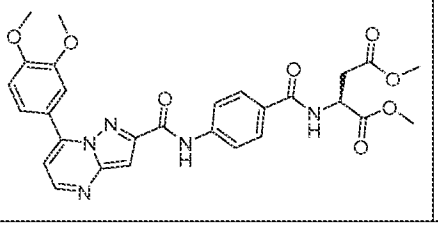
24		N-(4-ethoxyphenyl)-7-(3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
25		methyl 4-(7-(3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
26		ethyl 1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclopropane-1-carboxylate
27		7-(3,4-dimethoxyphenyl)-N-(4-(dimethylamino)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
28		ethyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)glycinate
29		1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclopropane-1-carboxylic acid

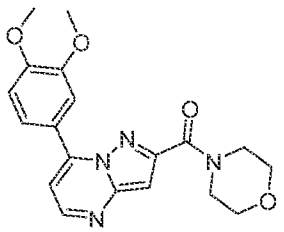
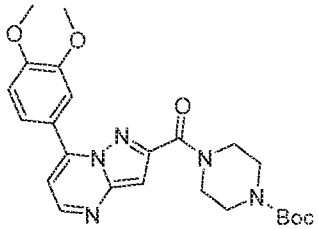
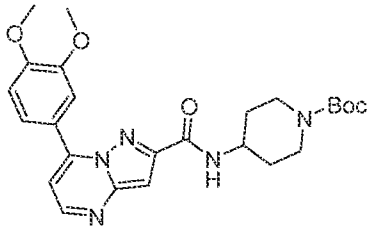
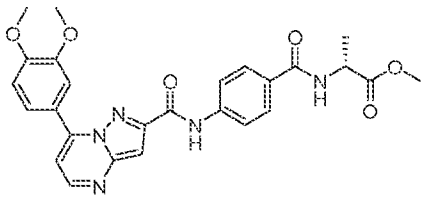
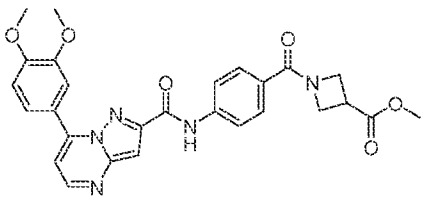
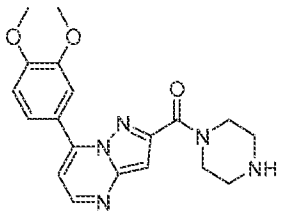
30		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)glycine
31		methyl 6-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)nicotinate
32		methyl 4-(7-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
33		methyl 4-(7-(3-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
34		ethyl 2-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenoxy)acetate
35		2-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenoxy)acetic acid

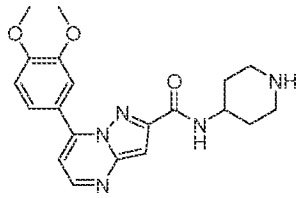
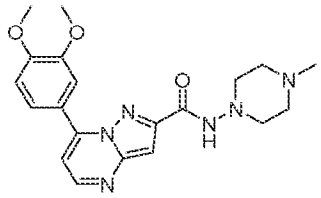
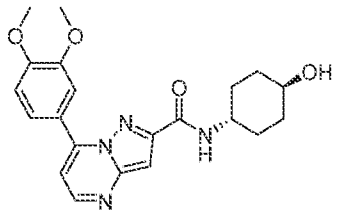
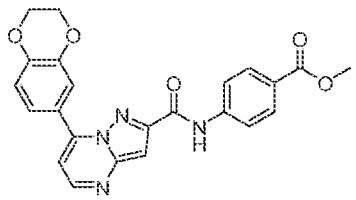
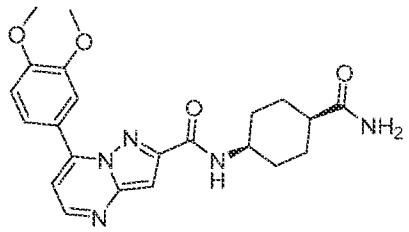
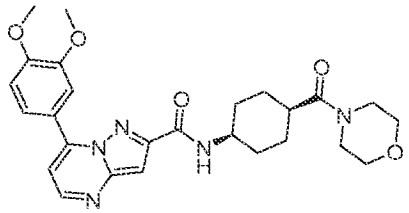
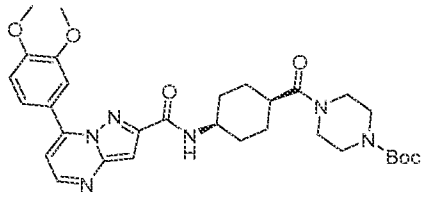
36		methyl 3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[1.1.1]pentane-1-carboxylate
37		3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[1.1.1]pentane-1-carboxylic acid
38		7-(3,4-dihydroxyphenyl)-N-(4-hydroxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
39		methyl 4-(7-(3-chloro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
40		methyl 4-(7-(3,4-dichlorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
41		7-(3,4-dimethoxyphenyl)-N-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

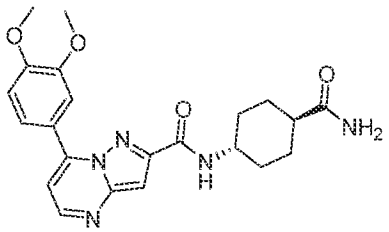
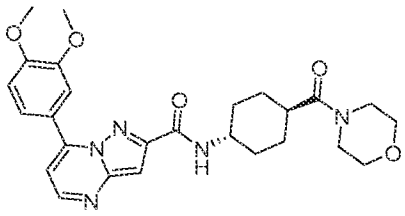
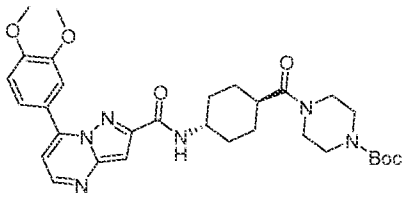
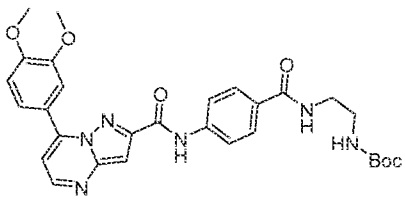
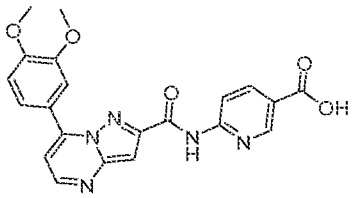
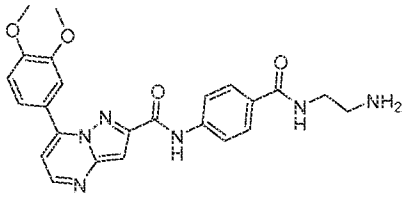
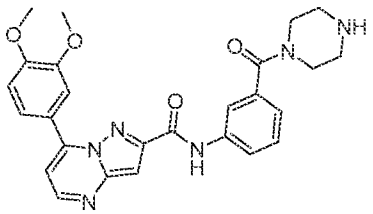
42		methyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-alaninate
43		methyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-serinate
44		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-alanine
45		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-serine
46		methyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-phenylalaninate
47		methyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-prolinate
48		N-(4-carbamoylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

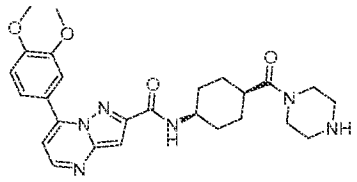
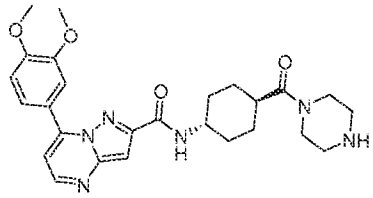
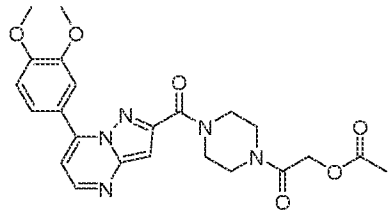
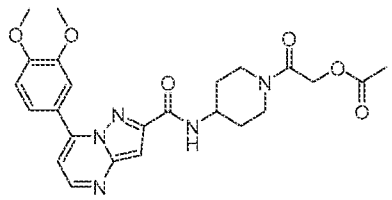
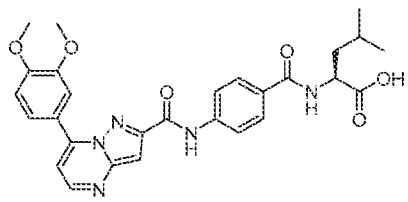
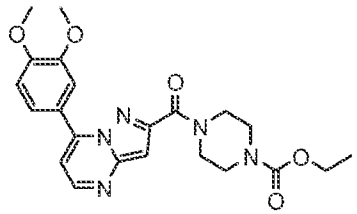
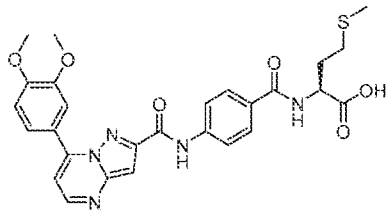
49		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-phenylalanine
50		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-proline
51		tert-butyl 4-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)piperazine-1-carboxylate
52		7-(3,4-dimethoxyphenyl)-N-(4-(piperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
53		7-(3,4-dimethoxyphenyl)-N-(4-((2-hydroxyethyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
54		N-(3-carbamoylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

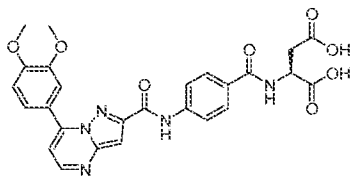
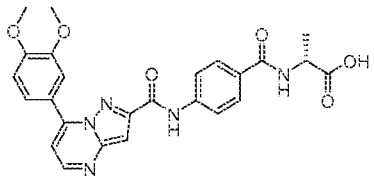
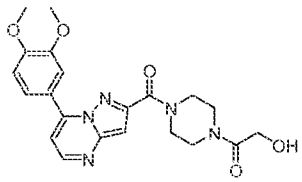
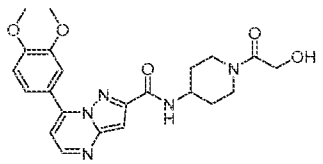
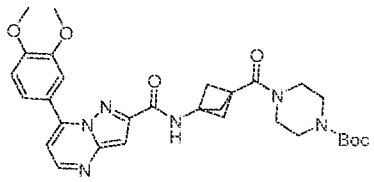
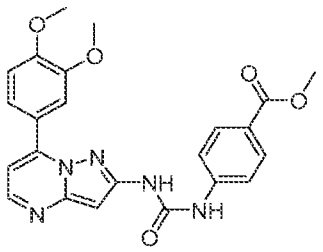
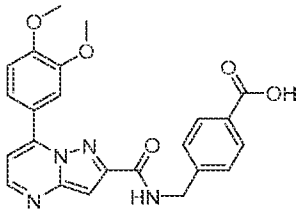
55		7-(3,4-dimethoxyphenyl)-N-(3-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
56		tert-butyl 4-(3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)piperazine-1-carboxylate
57		methyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-leucinate
58		methyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-valinate
59		methyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-methioninate
60		dimethyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-L-aspartate

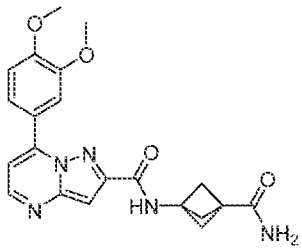
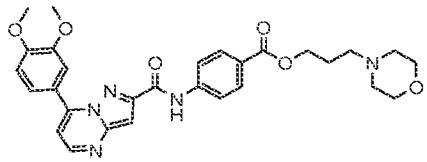
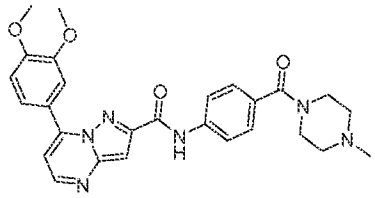
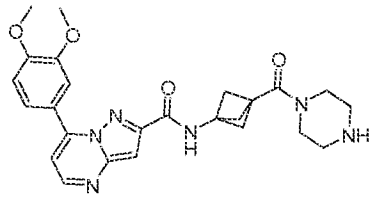
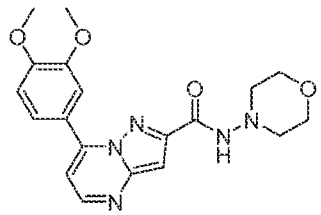
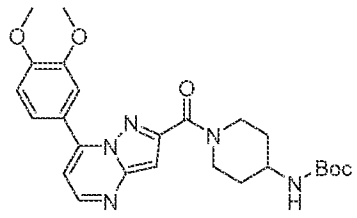
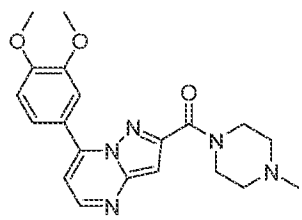
61		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(morpholino)methanone
62		tert-butyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)piperazine-1-carboxylate
63		tert-butyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)piperidine-1-carboxylate
64		methyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-D-alaninate
65		methyl 1-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)azetidine-3-carboxylate
66		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(piperazin-1-yl)methanone

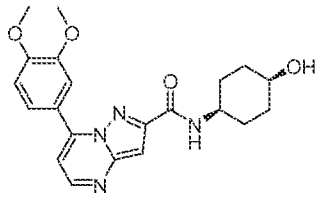
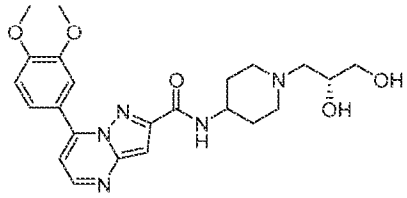
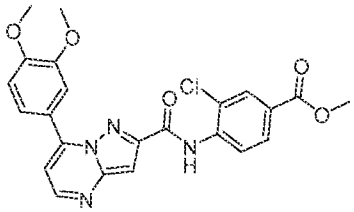
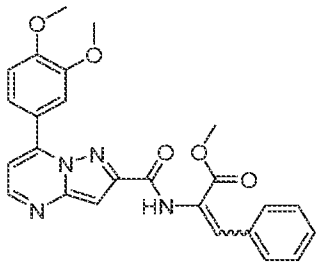
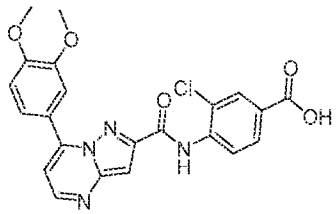
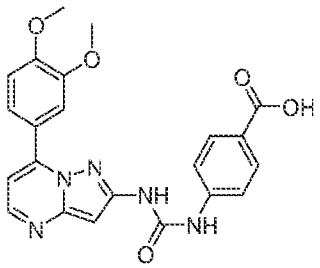
67		7-(3,4-dimethoxyphenyl)-N-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
68		7-(3,4-dimethoxyphenyl)-N-(4-methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
69		7-(3,4-dimethoxyphenyl)-N-((1R,4R)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
70		methyl 4-(7-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
71		N-((1S,4S)-4-carbamoylcyclohexyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
72		7-(3,4-dimethoxyphenyl)-N-((1S,4S)-4-(morpholine-4-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
73		tert-butyl 4-((1S,4S)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carbonyl)piperazine-1-carboxylate

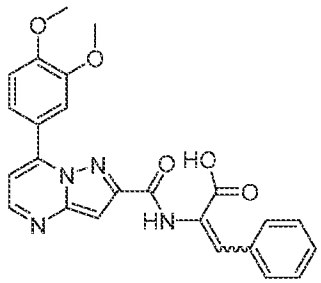
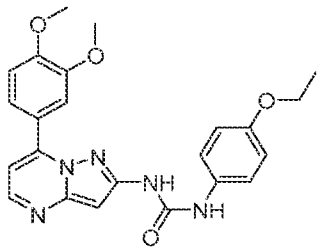
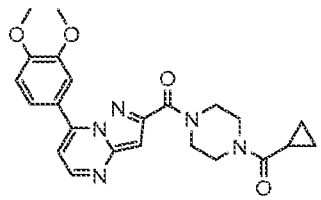
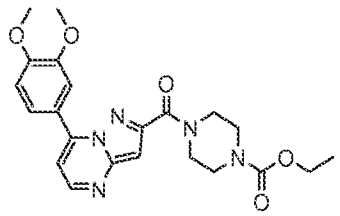
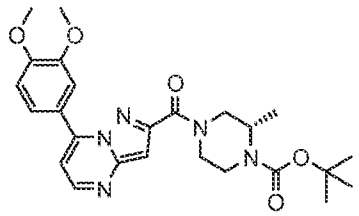
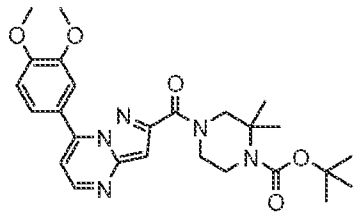
74		N-((1R,4R)-4-carbamoylcyclohexyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
75		7-(3,4-dimethoxyphenyl)-N-((1R,4R)-4-(morpholine-4-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
76		tert-butyl 4-((1R,4R)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carbonyl)piperazine-1-carboxylate
77		tert-butyl (2-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzamido)ethyl)carbamate
78		6-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)nicotinic acid
79		N-(4-((2-aminoethyl)carbamoyl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
80		7-(3,4-dimethoxyphenyl)-N-(3-(piperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

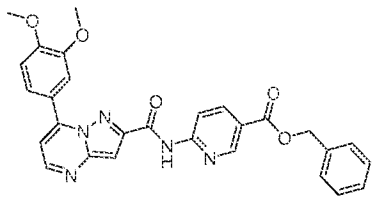
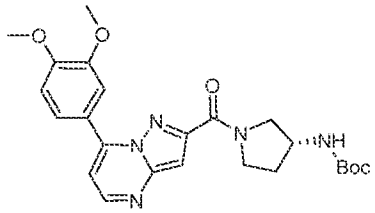
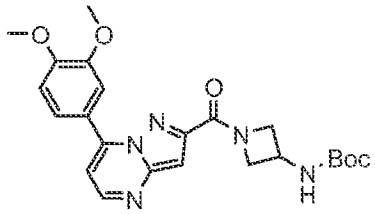
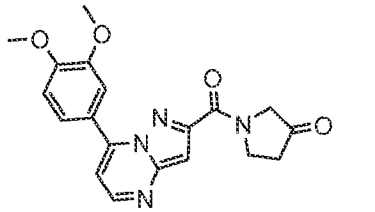
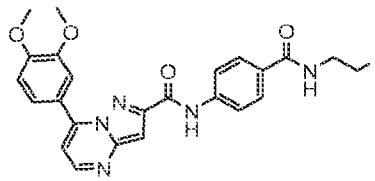
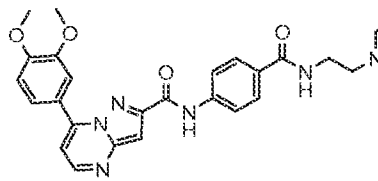
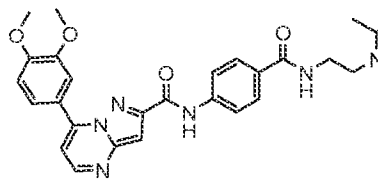
81		7-(3,4-dimethoxyphenyl)-N-((1S,4S)-4-(piperazine-1-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
82		7-(3,4-dimethoxyphenyl)-N-((1R,4R)-4-(piperazine-1-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
83		2-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)piperazin-1-yl)-2-oxoethyl acetate
84		2-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)piperidin-1-yl)-2-oxoethyl acetate
85		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-*L*-leucine
86		ethyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)piperazine-1-carboxylate
87		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-*L*-methionine

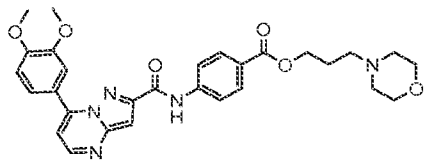
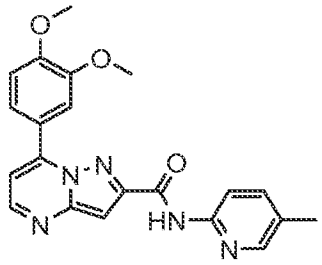
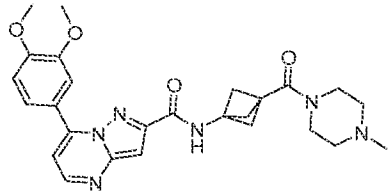
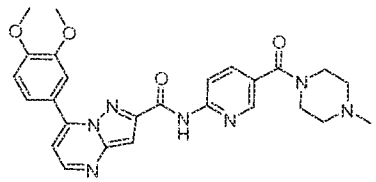
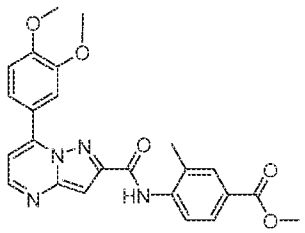
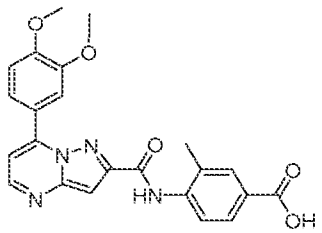
88		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-*L*-aspartic acid
89		(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)-D-alanine
90		1-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)piperazin-1-yl)-2-hydroxyethan-1-one
91		7-(3,4-dimethoxyphenyl)-N-(1-(2-hydroxyacetyl)piperidin-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
92		tert-butyl 4-(3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[1.1.1]pentane-1-carbonyl)piperazine-1-carboxylate
93		methyl 4-(3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)ureido)benzoate
94		4-((7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)methyl)benzoic acid

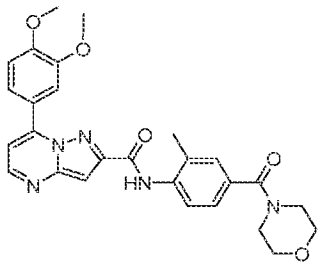
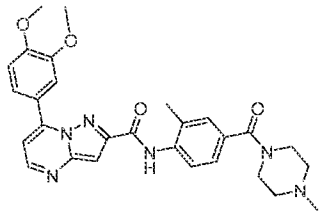
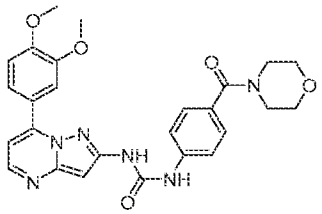
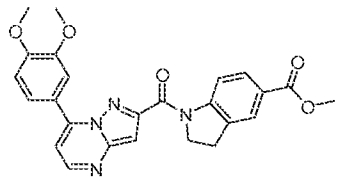
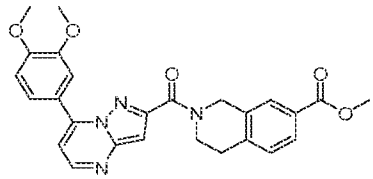
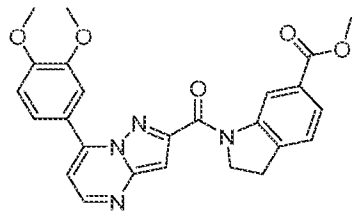
95		N-(3-carbamoylbicyclo[1.1.1]pentan-1-yl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
96		3-morpholinopropyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
97		7-(3,4-dimethoxyphenyl)-N-(4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
98		7-(3,4-dimethoxyphenyl)-N-(3-(piperazine-1-carbonyl)bicyclo[1.1.1]pentan-1-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
99		7-(3,4-dimethoxyphenyl)-N-morpholinopyrazolo[1,5-a]pyrimidine-2-carboxamide
100		tert-butyl (1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)piperidin-4-yl)carbamate
101		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-methylpiperazin-1-yl)methanone

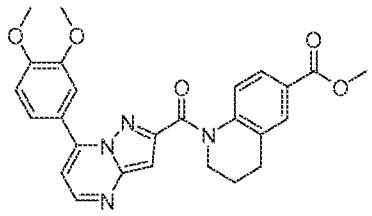
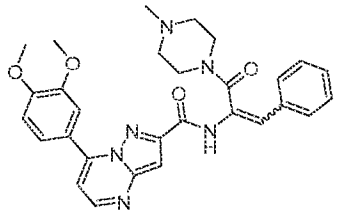
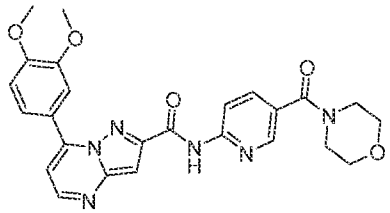
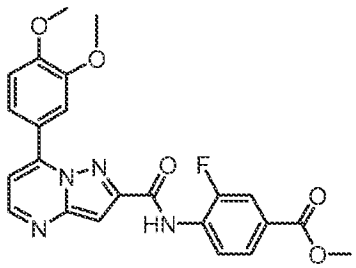
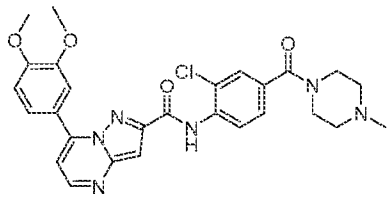
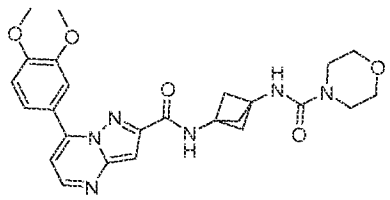
102		7-(3,4-dimethoxyphenyl)-N-((1S,4S)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
103		(R)-N-(1-(2,3-dihydroxypropyl)piperidin-4-yl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
104		methyl 3-chloro-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
105		methyl 2-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-phenylacrylate
106		3-chloro-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoic acid
107		4-(3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)ureido)benzoic acid

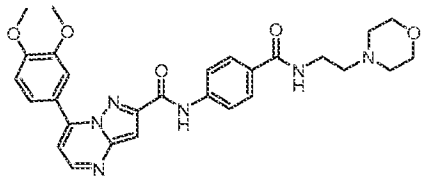
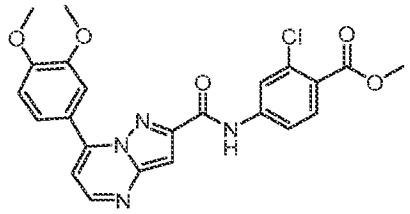
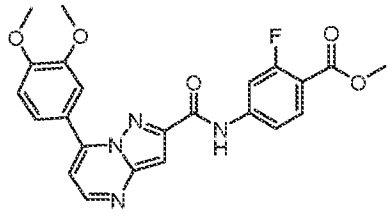
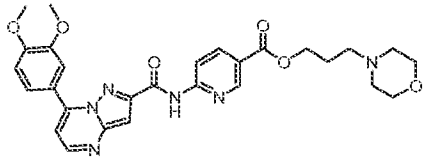
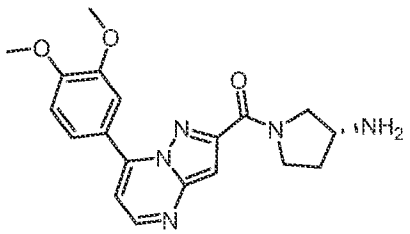
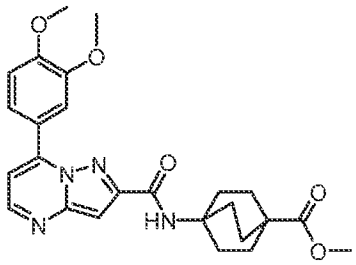
108		2-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-phenylacrylic acid
109		1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-(4-ethoxyphenyl)urea
110		(4-(cyclopropanecarbonyl)piperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
111		ethyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)piperazine-1-carboxylate
112		tert-butyl (S)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2-methylpiperazine-1-carboxylate
113		tert-butyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2,2-dimethylpiperazine-1-carboxylate

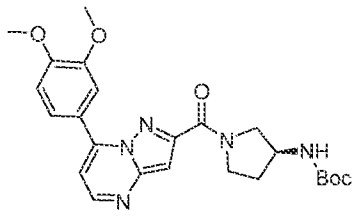
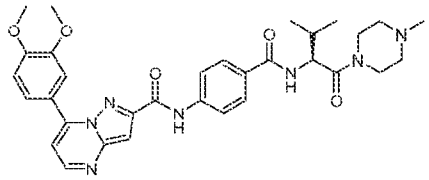
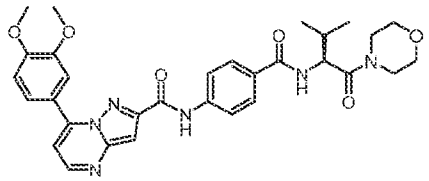
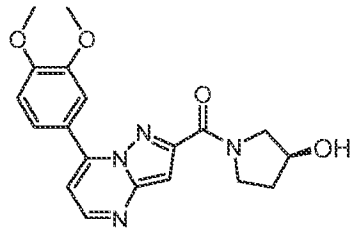
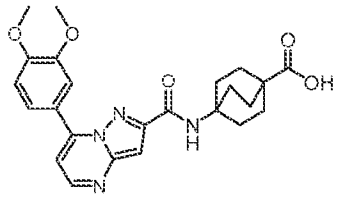
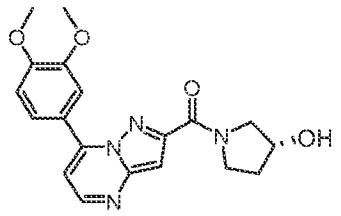
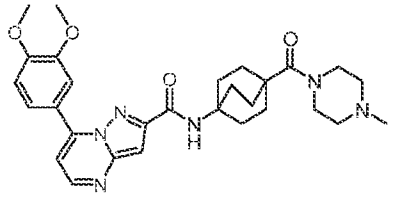
114		benzyl 6-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)nicotinate
115		tert-butyl (R)-(1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)pyrrolidin-3-yl)carbamate
116		tert-butyl (1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)azetidin-3-yl)carbamate
117		1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)pyrrolidin-3-one
118		7-(3,4-dimethoxyphenyl)-N-(4-((2-(dimethylamino)ethyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
119		7-(3,4-dimethoxyphenyl)-N-(4-((2-(piperidin-1-yl)ethyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
120		N-(4-((2-(diisopropylamino)ethyl)carbamoyl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

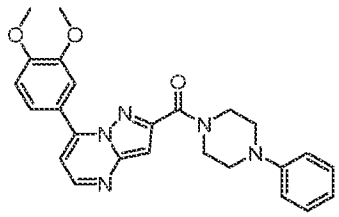
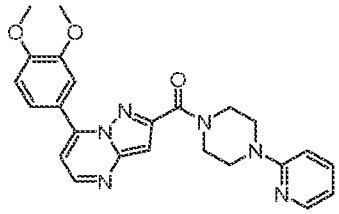
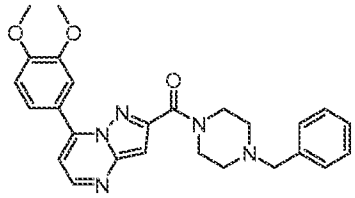
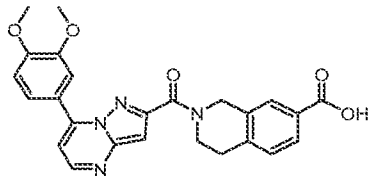
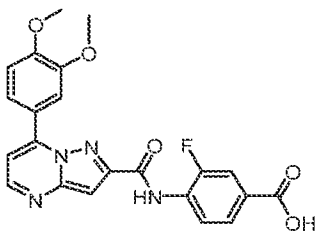
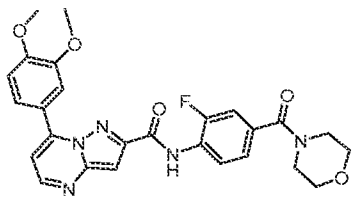
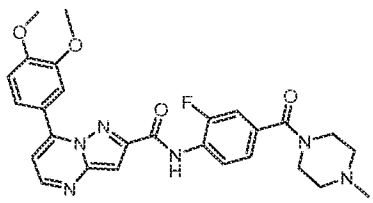
121		3-morpholinopropyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
122		7-(3,4-dimethoxyphenyl)-N-(5-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
123		7-(3,4-dimethoxyphenyl)-N-(3-(4-methylpiperazine-1-carbonyl)bicyclo[1.1.1]pentan-1-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
124		7-(3,4-dimethoxyphenyl)-N-(5-(4-methylpiperazine-1-carbonyl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
125		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-methylbenzoate
126		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-methylbenzoic acid

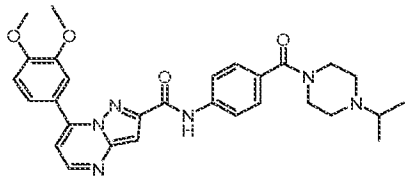
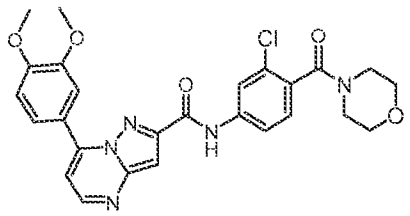
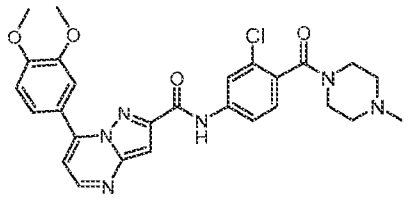
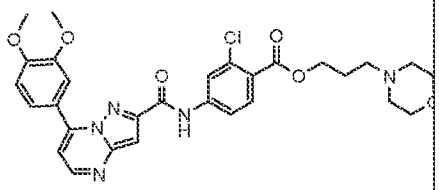
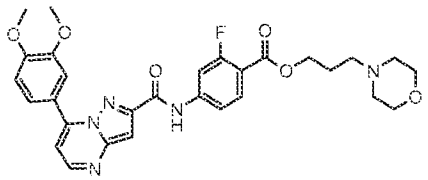
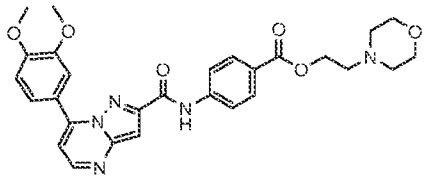
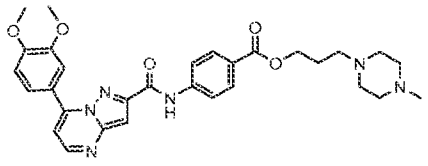
127		7-(3,4-dimethoxyphenyl)-N-(2-methyl-4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
128		7-(3,4-dimethoxyphenyl)-N-(2-methyl-4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
129		1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-(4-(morpholine-4-carbonyl)phenyl)urea
130		methyl 1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)indoline-5-carboxylate
131		methyl 2-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate
132		methyl 1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)indoline-6-carboxylate

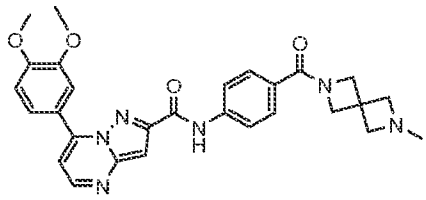
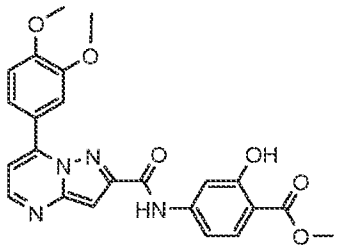
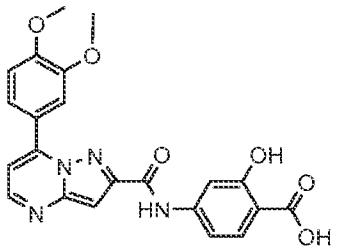
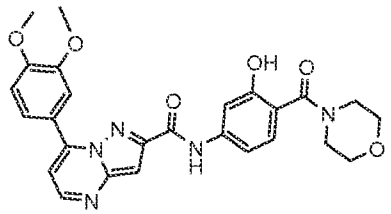
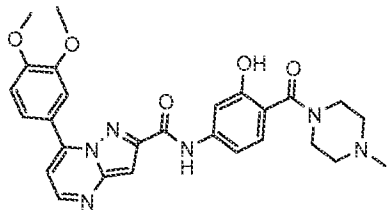
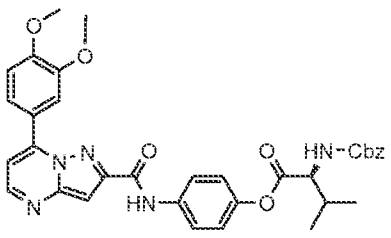
133		methyl 1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate
134		7-(3,4-dimethoxyphenyl)-N-(3-(4-methylpiperazin-1-yl)-3-oxo-1-phenylprop-1-en-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
135		7-(3,4-dimethoxyphenyl)-N-(5-(morpholine-4-carbonyl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
136		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-fluorobenzoate
137		N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
138		N-(3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[1.1.1]pentan-1-yl)morpholine-4-carboxamide

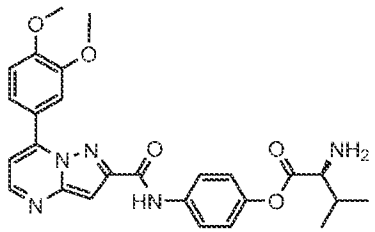
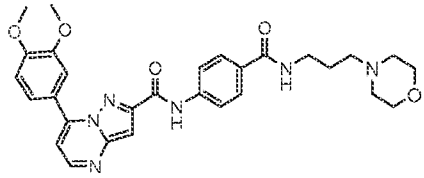
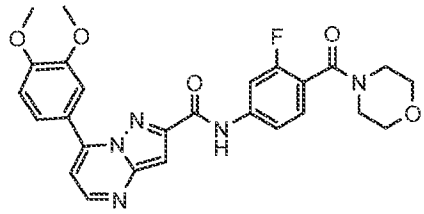
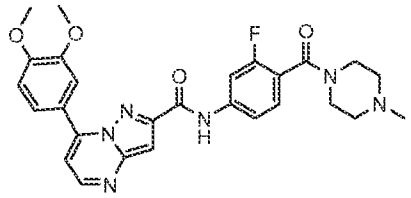
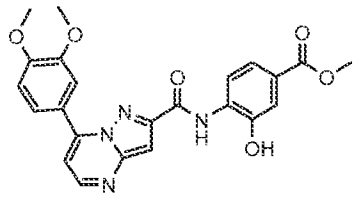
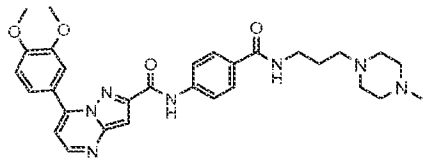
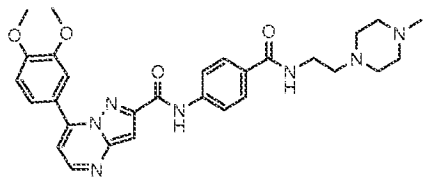
139		7-(3,4-dimethoxyphenyl)-N-(4-((2-morpholinoethyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
140		methyl 2-chloro-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
141		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-fluorobenzoate
142		3-morpholinopropyl 6-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)nicotinate
143		(R)-(3-aminopyrrolidin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
144		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[2.2.2]octane-1-carboxylate

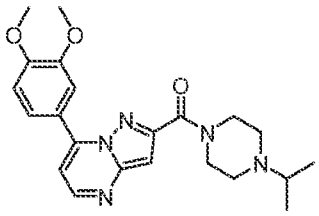
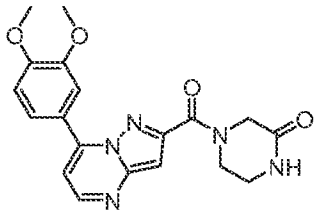
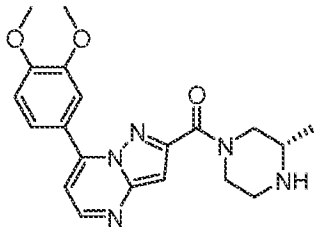
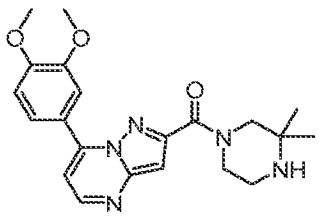
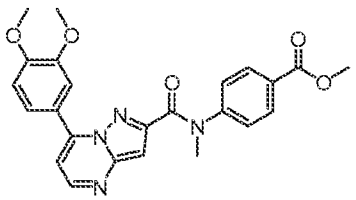
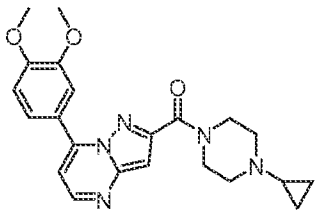
145		tert-butyl (S)-(1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)pyrrolidin-3-yl)carbamate
146		(S)-7-(3,4-dimethoxyphenyl)-N-(4-((3-methyl-1-(4-methylpiperazin-1-yl)-1-oxobutan-2-yl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
147		(S)-7-(3,4-dimethoxyphenyl)-N-(4-((3-methyl-1-morpholino-1-oxobutan-2-yl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
148		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone
149		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[2.2.2]octane-1-carboxylic acid
150		(R)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone
151		7-(3,4-dimethoxyphenyl)-N-(4-(4-methylpiperazine-1-carbonyl)bicyclo[2.2.2]octan-1-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

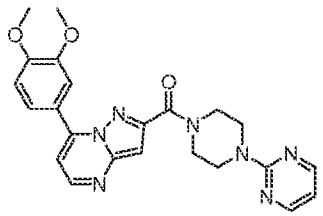
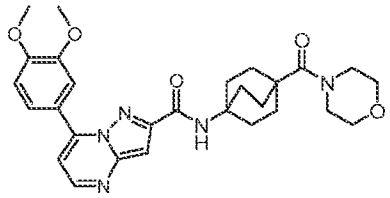
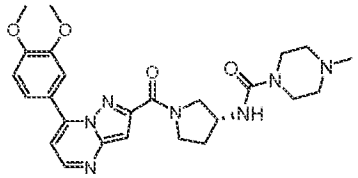
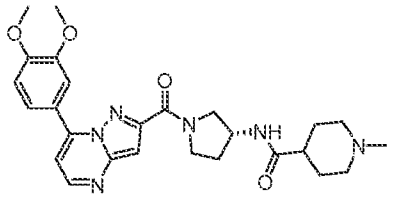
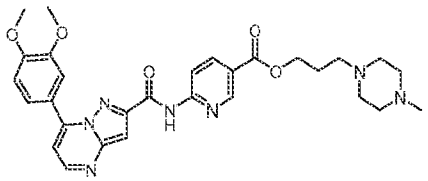
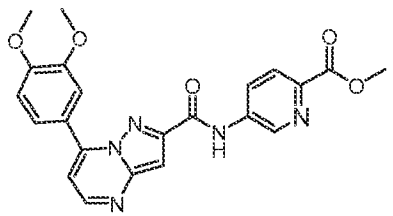
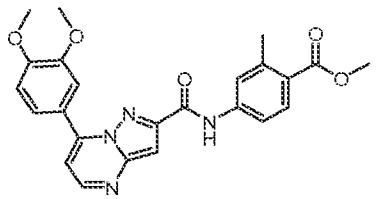
152		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-phenylpiperazin-1-yl)methanone
153		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone
154		(4-benzylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
155		2-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid
156		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-fluorobenzoic acid
157		7-(3,4-dimethoxyphenyl)-N-(2-fluoro-4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
158		7-(3,4-dimethoxyphenyl)-N-(2-fluoro-4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

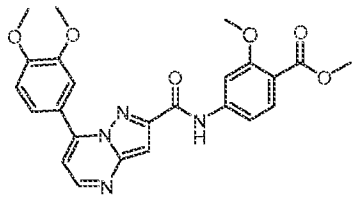
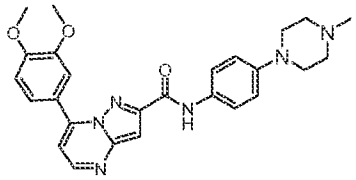
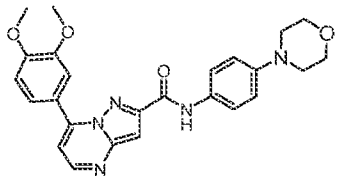
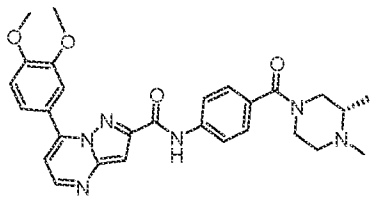
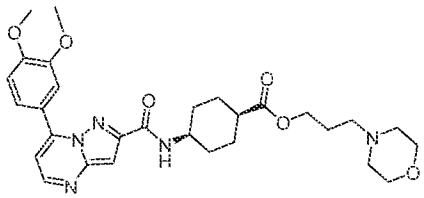
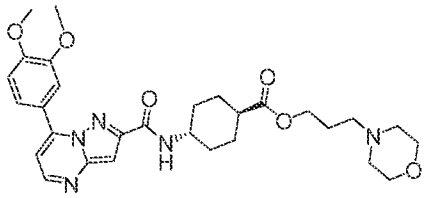
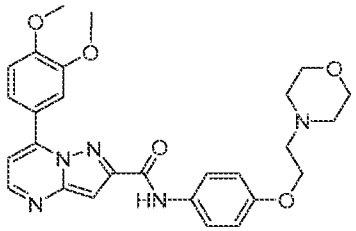
159		7-(3,4-dimethoxyphenyl)-N-(4-(4-isopropylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
160		N-(3-chloro-4-(morpholine-4-carbonyl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
161		N-(3-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
162		3-morpholinopropyl 2-chloro-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
163		3-morpholinopropyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-fluorobenzoate
164		2-morpholinoethyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
165		3-(4-methylpiperazin-1-yl)propyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate

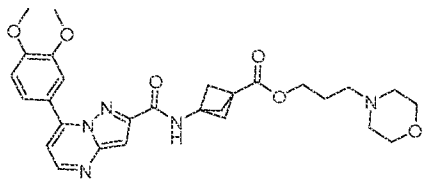
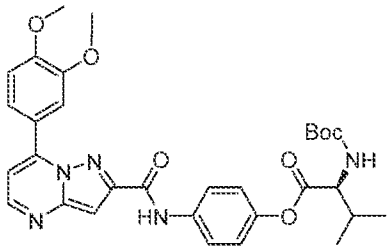
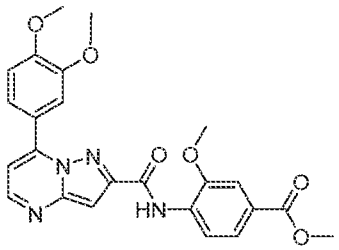
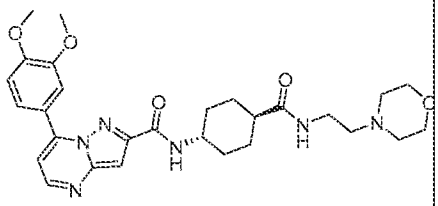
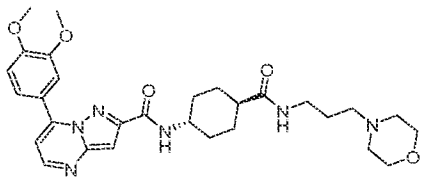
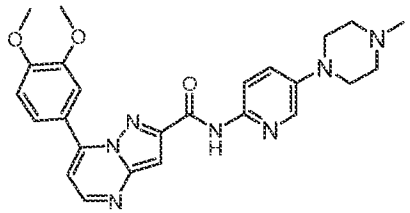
166		7-(3,4-dimethoxyphenyl)-N-(4-(6-methyl-2,6-diazaspiro[3.3]heptane-2-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
167		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-hydroxybenzoate
168		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-hydroxybenzoic acid
169		7-(3,4-dimethoxyphenyl)-N-(3-hydroxy-4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
170		7-(3,4-dimethoxyphenyl)-N-(3-hydroxy-4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
171		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl ((benzyloxy)carbonyl)-L-valinate

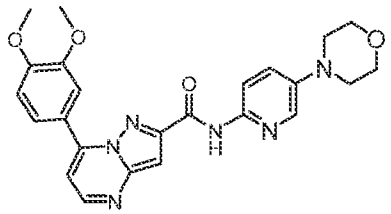
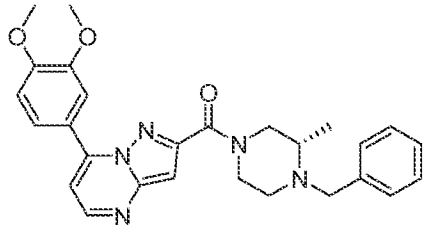
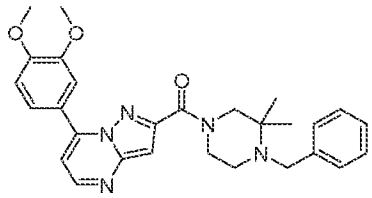
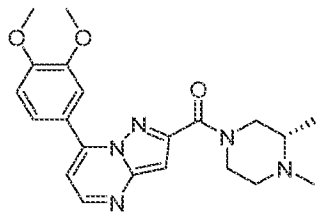
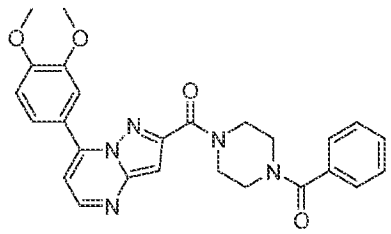
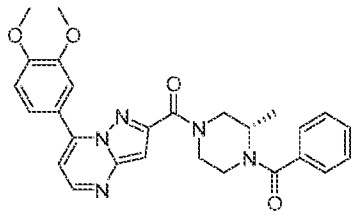
172		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl L-valinate
173		7-(3,4-dimethoxyphenyl)-N-(4-((3-morpholinopropyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
174		7-(3,4-dimethoxyphenyl)-N-(3-fluoro-4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
175		7-(3,4-dimethoxyphenyl)-N-(3-fluoro-4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
176		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-hydroxybenzoate
177		7-(3,4-dimethoxyphenyl)-N-(4-((3-(4-methylpiperazin-1-yl)propyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
178		7-(3,4-dimethoxyphenyl)-N-(4-((2-(4-methylpiperazin-1-yl)ethyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

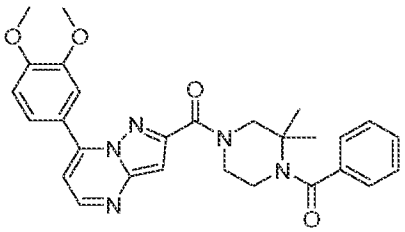
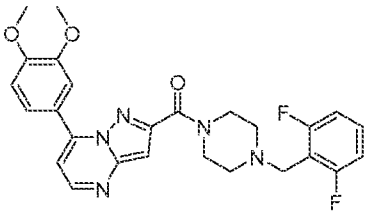
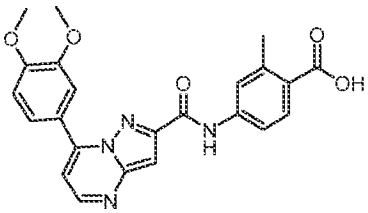
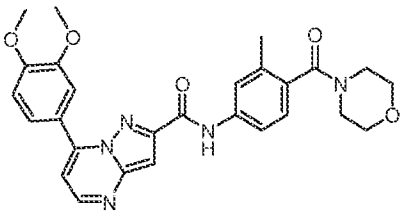
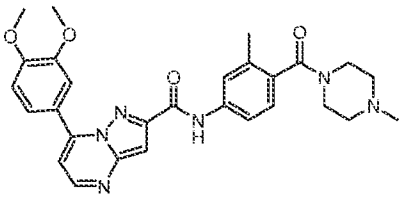
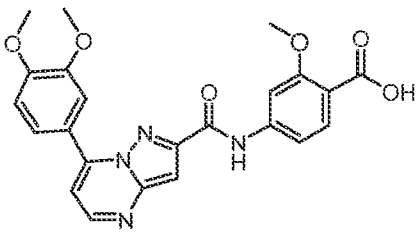
179		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-isopropylpiperazin-1-yl)methanone
180		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)piperazin-2-one
181		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methylpiperazin-1-yl)methanone
182		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3,3-dimethylpiperazin-1-yl)methanone
183		methyl 4-(7-(3,4-dimethoxyphenyl)-N-methylpyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
184		(4-cyclopropylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone

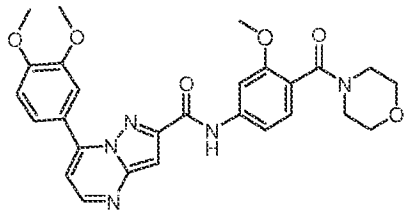
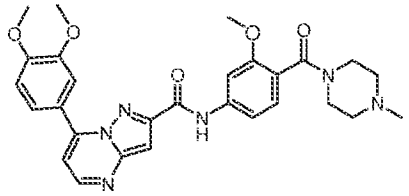
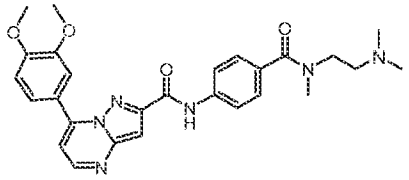
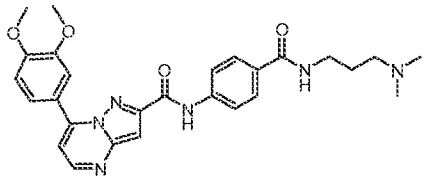
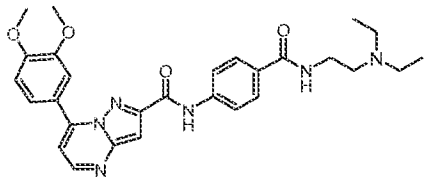
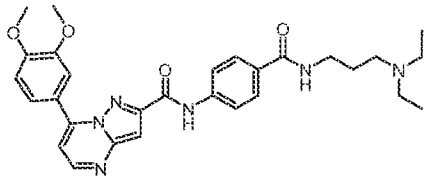
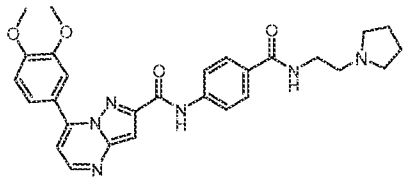
185		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone
186		7-(3,4-dimethoxyphenyl)-N-(4-(morpholine-4-carbonyl)bicyclo[2.2.2]octan-1-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
187		(R)-N-(1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)pyrrolidin-3-yl)-4-methylpiperazine-1-carboxamide
188		(R)-N-(1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)pyrrolidin-3-yl)-1-methylpiperidine-4-carboxamide
189		3-(4-methylpiperazin-1-yl)propyl 6-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)nicotinate
190		methyl 5-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)picolinate
191		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-methylbenzoate

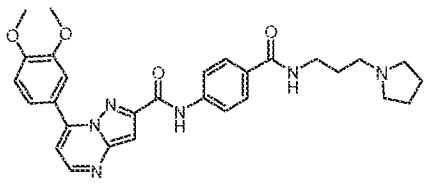
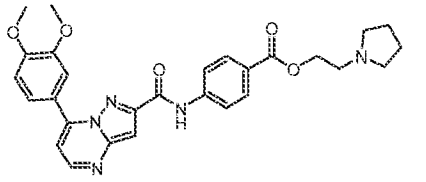
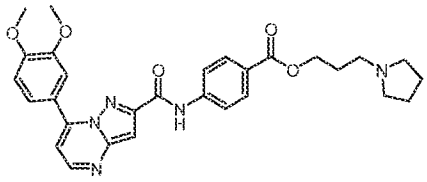
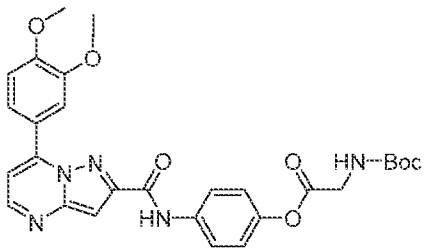
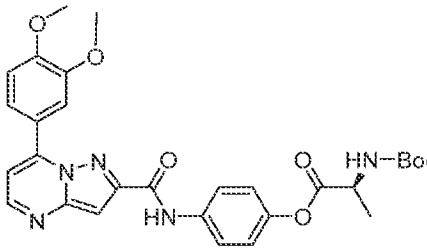
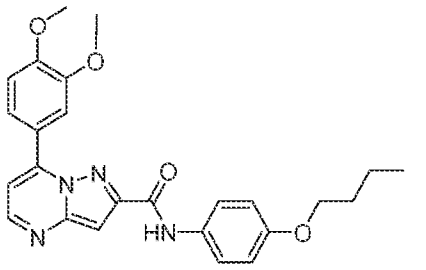
192		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-methoxybenzoate
193		7-(3,4-dimethoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
194		7-(3,4-dimethoxyphenyl)-N-(4-morpholinophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
195		(S)-7-(3,4-dimethoxyphenyl)-N-(4-(3,4-dimethylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
196		3-morpholinopropyl (1s,4s)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
197		3-morpholinopropyl (1r,4r)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
198		7-(3,4-dimethoxyphenyl)-N-(4-(2-morpholinoethoxy)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

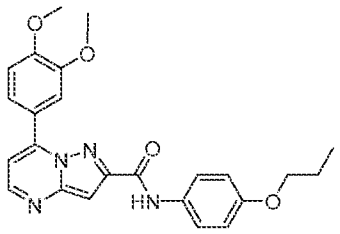
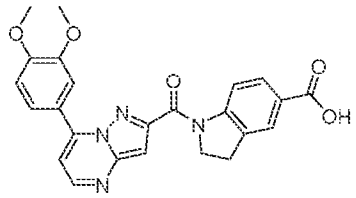
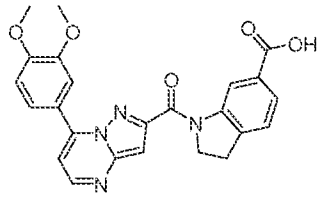
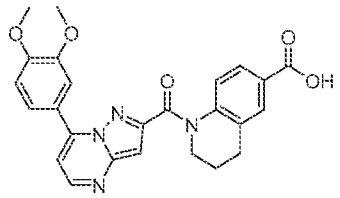
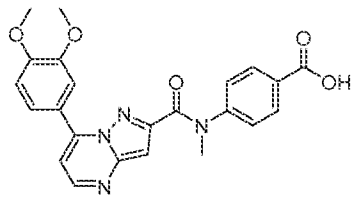
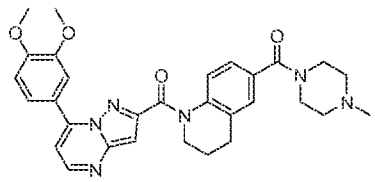
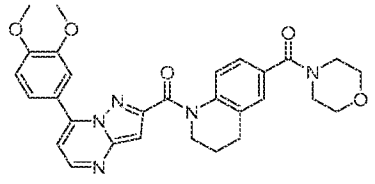
199		3-morpholinopropyl 3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[1.1.1]pentane-1-carboxylate
200		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl (tert-butoxycarbonyl)-L-valinate
201		methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-methoxybenzoate
202		7-(3,4-dimethoxyphenyl)-N-((1r,4r)-4-((2-morpholinoethyl)carbamoyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
203		7-(3,4-dimethoxyphenyl)-N-((1r,4r)-4-((3-morpholinopropyl)carbamoyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
204		7-(3,4-dimethoxyphenyl)-N-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

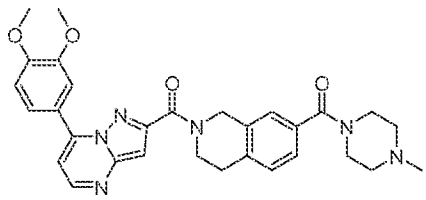
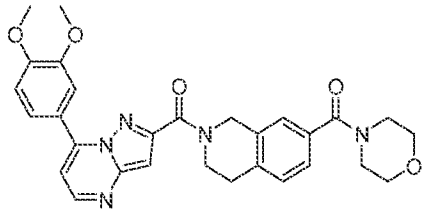
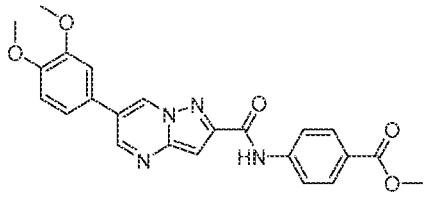
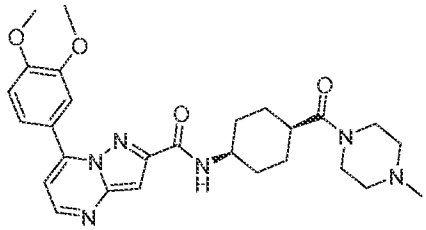
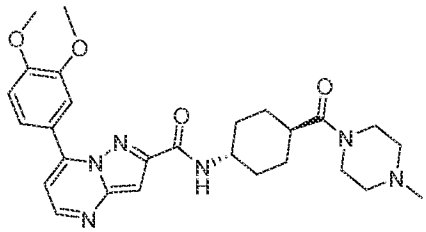
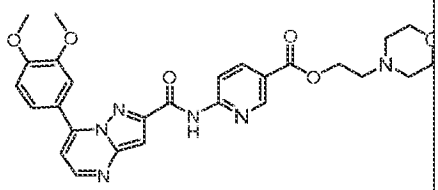
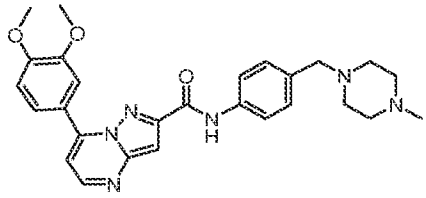
205		7-(3,4-dimethoxyphenyl)-N-(5-morpholinopyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
206		(S)-(4-benzyl-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
207		(4-benzyl-3,3-dimethylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
208		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3,4-dimethylpiperazin-1-yl)methanone
209		(4-benzoylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
210		(S)-(4-benzoyl-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone

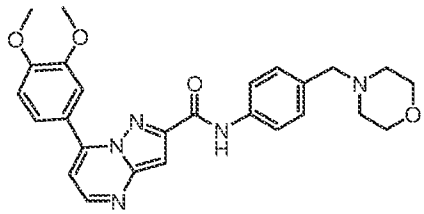
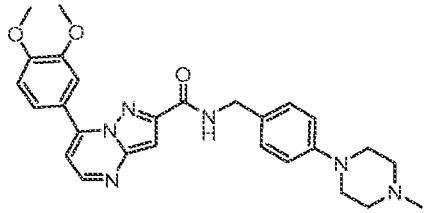
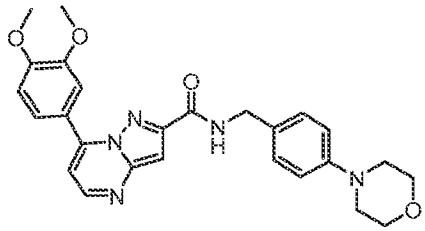
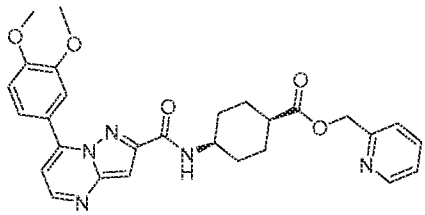
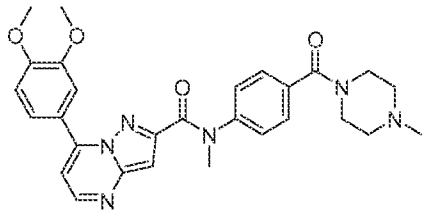
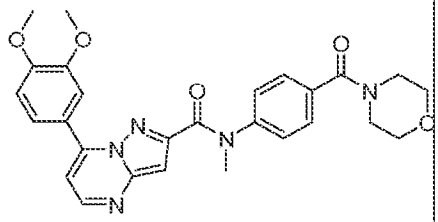
211		(4-benzoyl-3,3-dimethylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
212		(4-(2,6-difluorobenzyl)piperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
213		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-methylbenzoic acid
214		7-(3,4-dimethoxyphenyl)-N-(3-methyl-4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
215		7-(3,4-dimethoxyphenyl)-N-(3-methyl-4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
216		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-methoxybenzoic acid

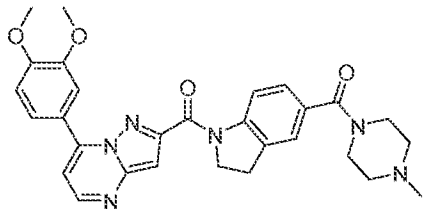
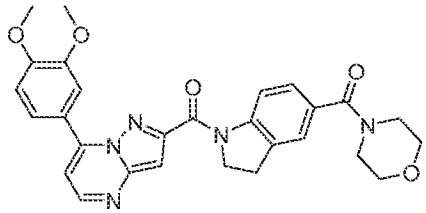
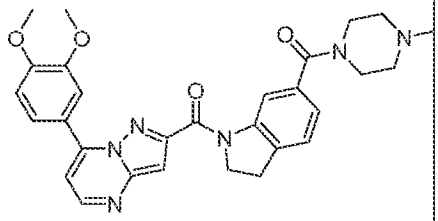
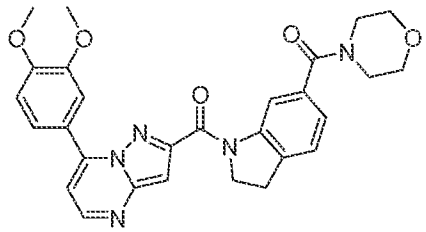
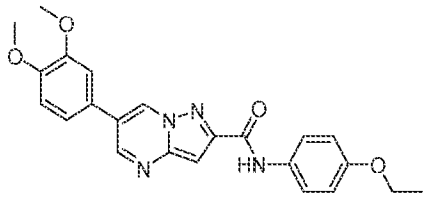
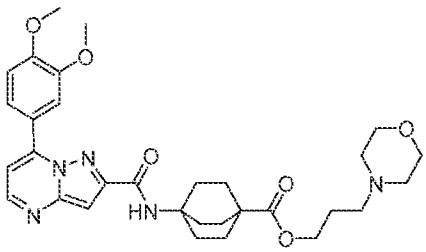
217		7-(3,4-dimethoxyphenyl)-N-(3-methoxy-4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
218		7-(3,4-dimethoxyphenyl)-N-(3-methoxy-4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
219		7-(3,4-dimethoxyphenyl)-N-(4-((2-(dimethylamino)ethyl)(methyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
220		7-(3,4-dimethoxyphenyl)-N-(4-((3-(dimethylamino)propyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
221		N-(4-((2-(diethylamino)ethyl)carbamoyl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
222		N-(4-((3-(diethylamino)propyl)carbamoyl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
223		7-(3,4-dimethoxyphenyl)-N-(4-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

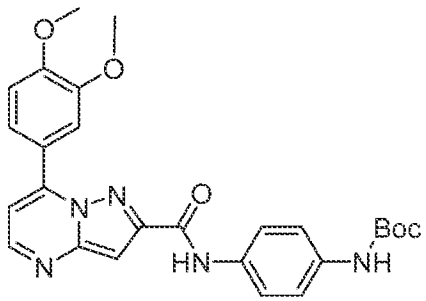
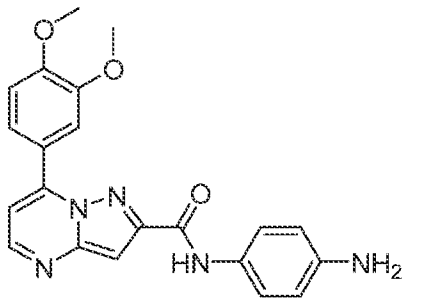
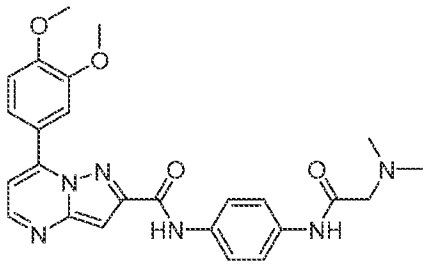
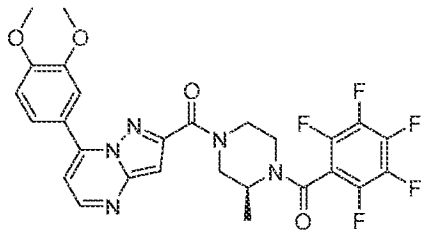
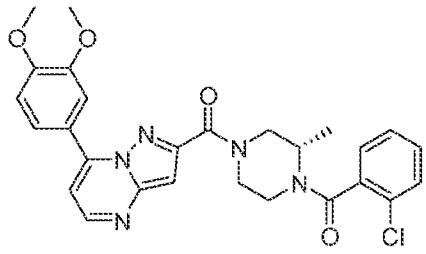
224		7-(3,4-dimethoxyphenyl)-N-(4-((3-(pyrrolidin-1-yl)propyl)carbamoyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
225		2-(pyrrolidin-1-yl)ethyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
226		3-(pyrrolidin-1-yl)propyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
227		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl (tert-butoxycarbonyl)glycinate
228		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl (tert-butoxycarbonyl)-*L*-alaninate
229		N-(4-butoxyphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

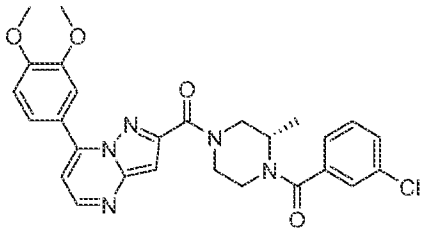
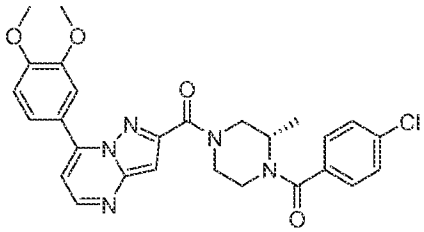
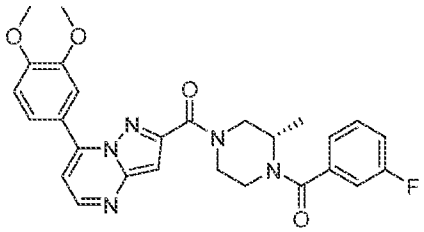
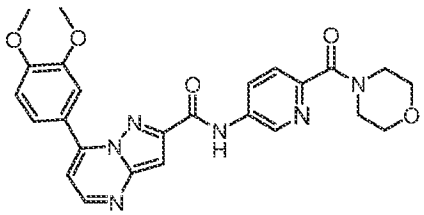
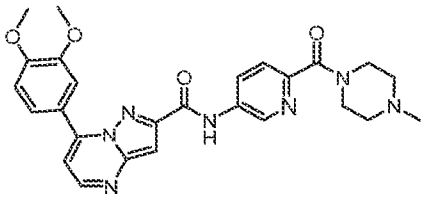
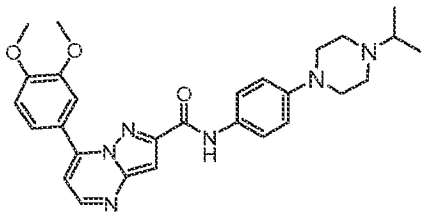
230		7-(3,4-dimethoxyphenyl)-N-(4-propoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
231		1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)indoline-5-carboxylic acid
232		1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)indoline-6-carboxylic acid
233		1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid
234		4-(7-(3,4-dimethoxyphenyl)-N-methylpyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoic acid
235		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(6-(4-methylpiperazine-1-carbonyl)-3,4-dihydroquinolin-1(2H)-yl)methanone
236		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(6-(morpholine-4-carbonyl)-3,4-dihydroquinolin-1(2H)-yl)methanone

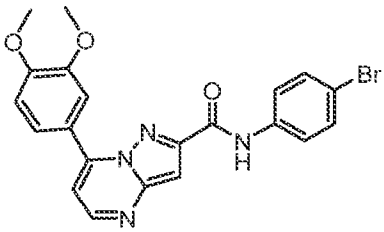
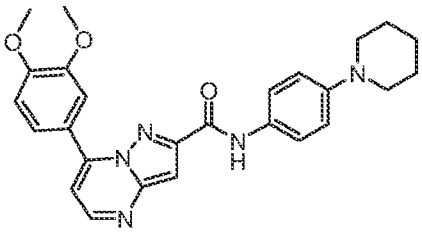
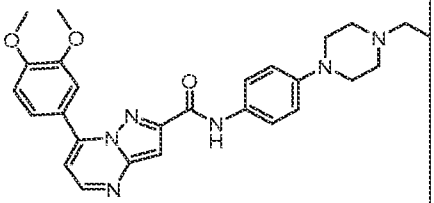
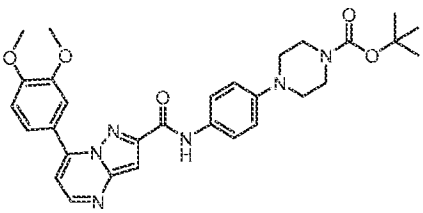
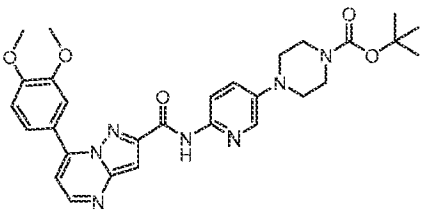
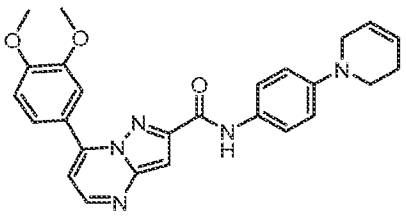
237		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(7-(4-methylpiperazine-1-carbonyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone
238		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(7-(morpholine-4-carbonyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone
239		7-(3,4-dimethoxyphenyl)-N-((1S,4S)-4-(4-methylpiperazine-1-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
240		7-(3,4-dimethoxyphenyl)-N-((1S,4S)-4-(4-methylpiperazine-1-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
241		7-(3,4-dimethoxyphenyl)-N-((1r,4r)-4-(4-methylpiperazine-1-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
242		2-morpholinoethyl 6-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)nicotinate
243		7-(3,4-dimethoxyphenyl)-N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

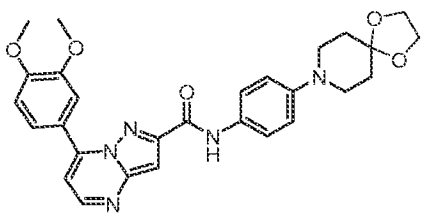
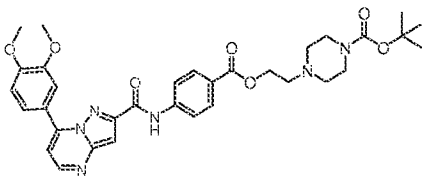
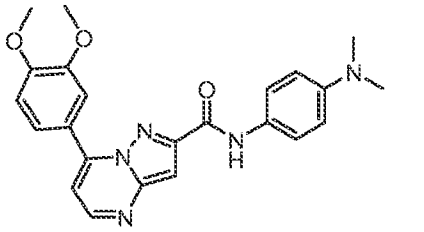
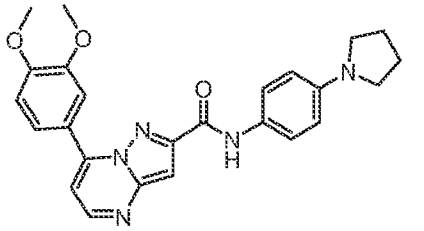
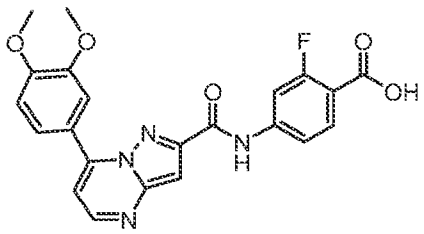
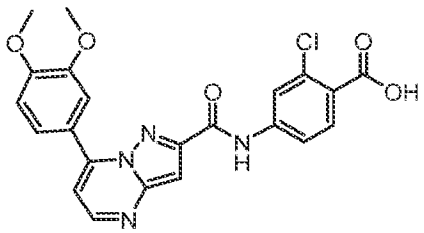
244		7-(3,4-dimethoxyphenyl)-N-(4-(morpholinomethyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
245		7-(3,4-dimethoxyphenyl)-N-(4-(4-methylpiperazin-1-yl)benzyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
246		7-(3,4-dimethoxyphenyl)-N-(4-morpholinobenzyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
247		pyridin-2-ylmethyl (1S,4S)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
248		7-(3,4-dimethoxyphenyl)-N-methyl-N-(4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
249		7-(3,4-dimethoxyphenyl)-N-methyl-N-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

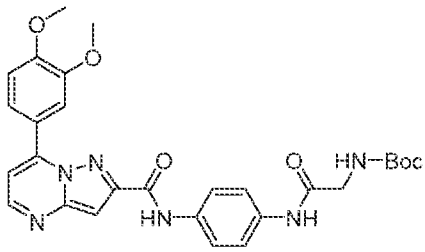
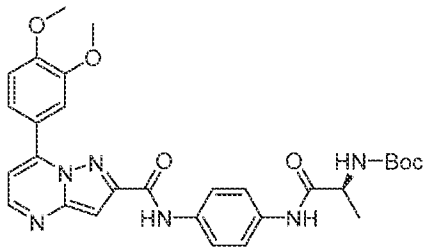
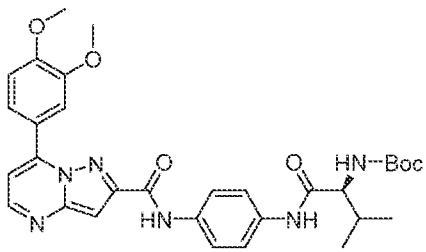
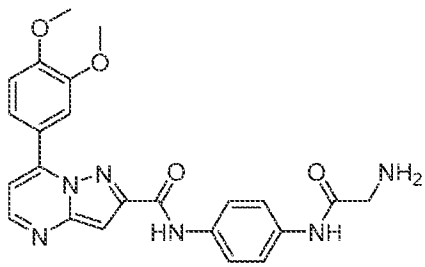
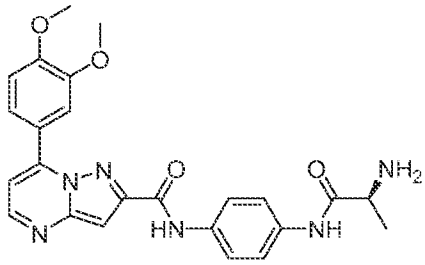
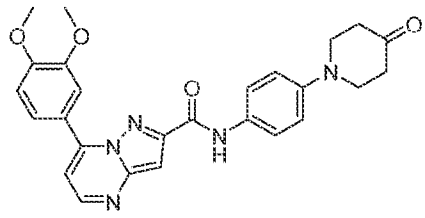
250		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(5-(4-methylpiperazine-1-carbonyl)indolin-1-yl)methanone
251		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(5-(morpholine-4-carbonyl)indolin-1-yl)methanone
252		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(6-(4-methylpiperazine-1-carbonyl)indolin-1-yl)methanone
253		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(6-(morpholine-4-carbonyl)indolin-1-yl)methanone
254		6-(3,4-dimethoxyphenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
255		3-morpholinopropyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[2.2.2]octane-1-carboxylate

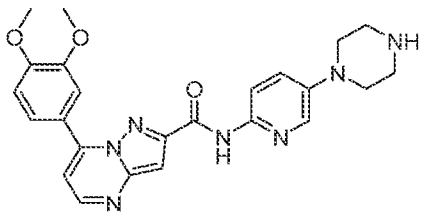
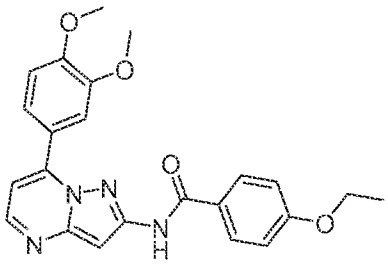
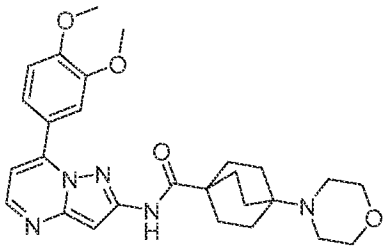
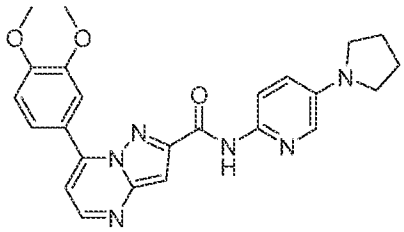
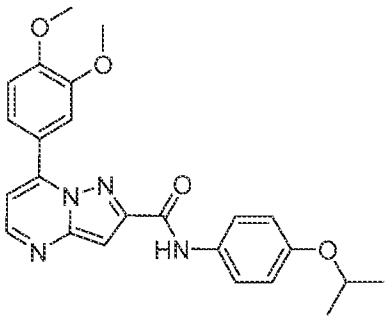
256		tert-butyl (4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl)carbamate
257		N-(4-aminophenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
258		7-(3,4-dimethoxyphenyl)-N-(4-(2-(dimethylamino)acetamido)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
259		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(perfluorobenzoyl)piperazin-1-yl)methanone
260		(S)-(4-(2-chlorobenzoyl)-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone

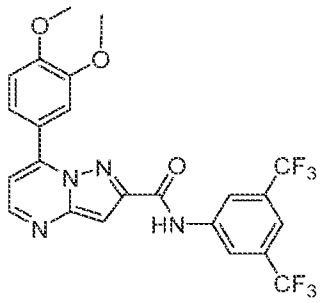
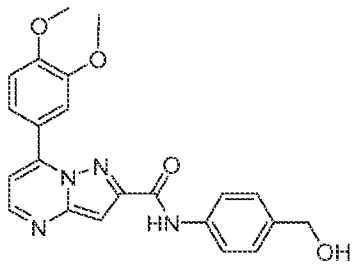
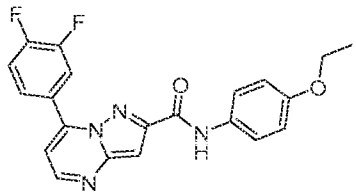
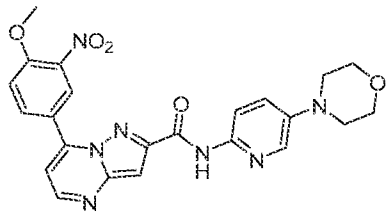
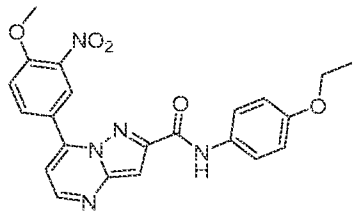
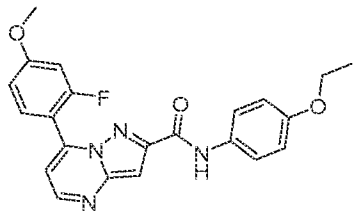
261		(S)-(4-(3-chlorobenzoyl)-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
262		(S)-(4-(4-chlorobenzoyl)-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
263		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(3-fluorobenzoyl)-3-methylpiperazin-1-yl)methanone
264		7-(3,4-dimethoxyphenyl)-N-(6-(morpholine-4-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
265		7-(3,4-dimethoxyphenyl)-N-(6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
266		7-(3,4-dimethoxyphenyl)-N-(4-(4-isopropylpiperazin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

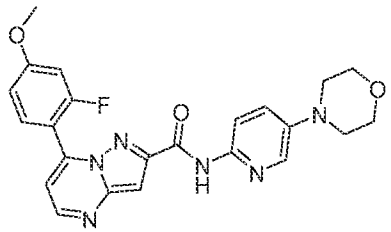
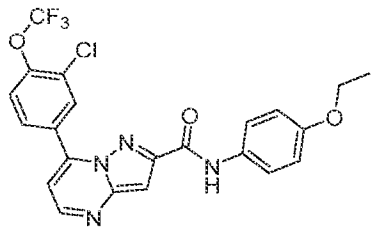
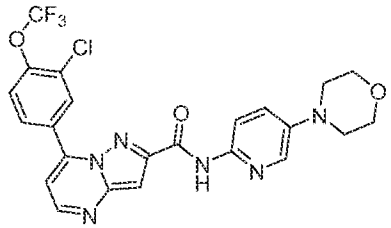
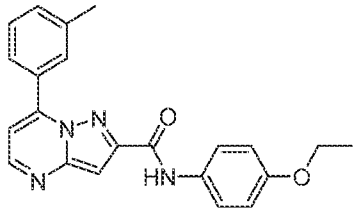
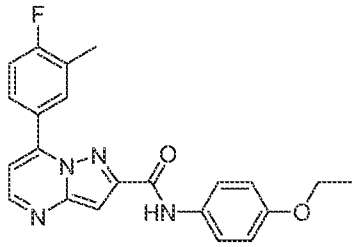
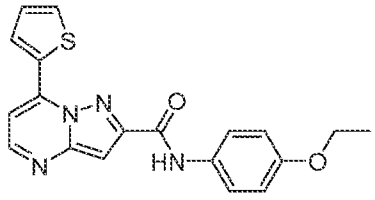
268		N-(4-bromophenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
269		7-(3,4-dimethoxyphenyl)-N-(4-(piperidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
270		7-(3,4-dimethoxyphenyl)-N-(4-(4-ethylpiperazin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
271		tert-butyl 4-(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl)piperazine-1-carboxylate
272		tert-butyl 4-(6-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)pyridin-3-yl)piperazine-1-carboxylate
273		N-(4-(3,6-dihydropyridin-1(2H)-yl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

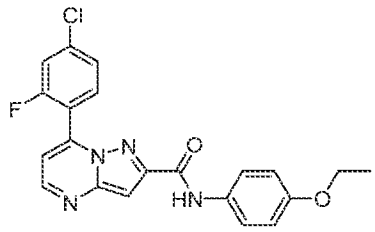
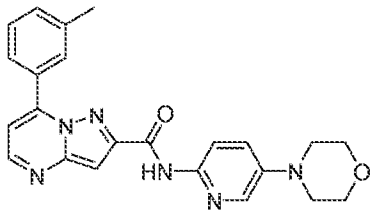
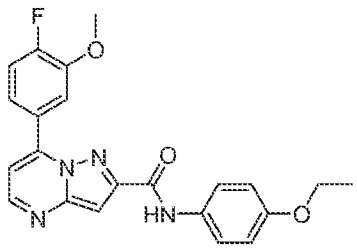
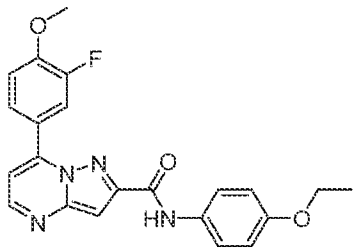
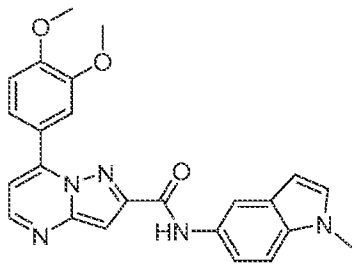
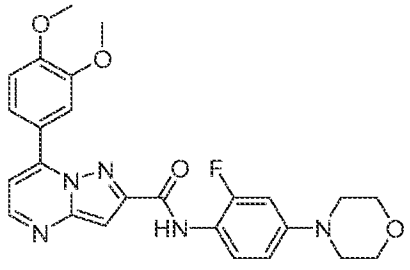
274		N-(4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
275		tert-butyl 4-(2-((4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoyl)oxy)ethyl)piperazine-1-carboxylate
276		7-(3,4-dimethoxyphenyl)-N-(4-(dimethylamino)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
277		7-(3,4-dimethoxyphenyl)-N-(4-(pyrrolidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
278		4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-2-fluorobenzoic acid
279		2-chloro-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoic acid

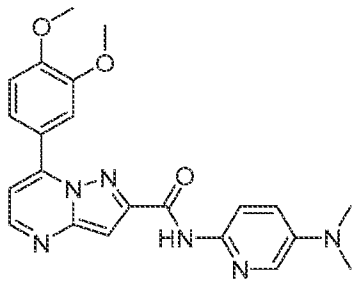
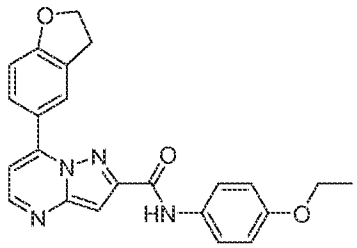
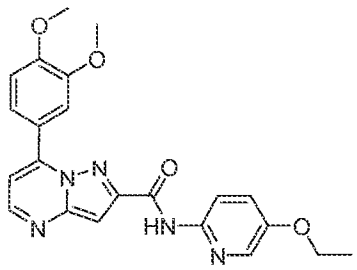
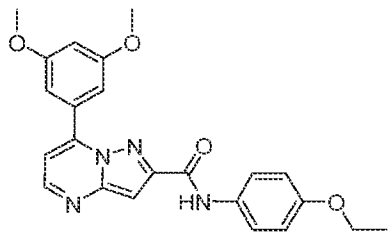
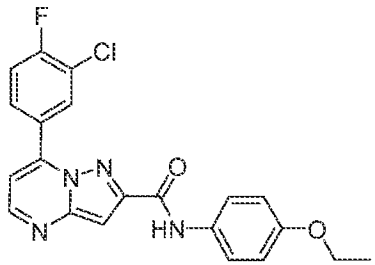
280		tert-butyl (2-((4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl)amino)-2-oxoethyl)carbamate
281		tert-butyl (S)-(1-((4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl)amino)-1-oxopropan-2-yl)carbamate
282		tert-butyl (S)-(1-((4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)phenyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate
283		N-(4-(2-aminoacetamido)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
284		(S)-N-(4-(2-aminopropanamido)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
285		7-(3,4-dimethoxyphenyl)-N-(4-(4-oxopiperidin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

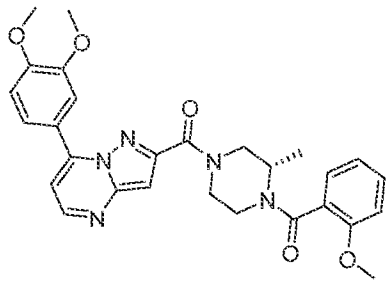
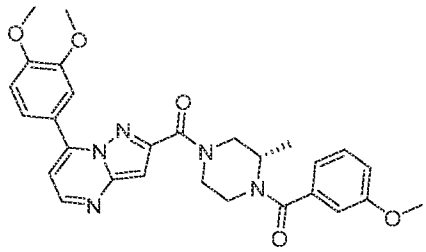
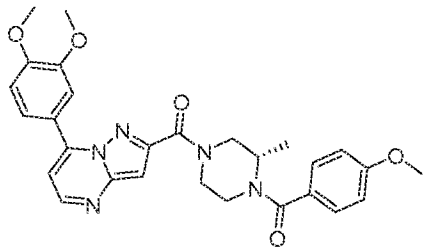
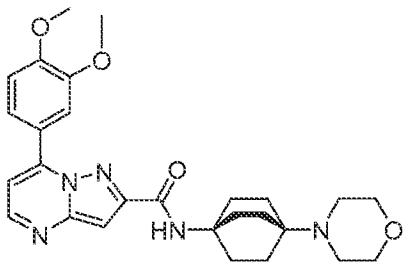
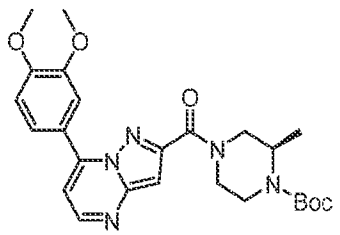
286		7-(3,4-dimethoxyphenyl)-N-(5-(piperazin-1-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
287		N-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)-4-ethoxybenzamide
288		N-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)-4-morpholinobicyclo[2.2.2]octane-1-carboxamide
289		7-(3,4-dimethoxyphenyl)-N-(5-(pyrrolidin-1-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
290		7-(3,4-dimethoxyphenyl)-N-(4-isopropoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

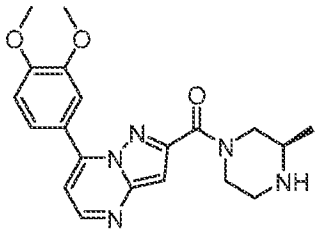
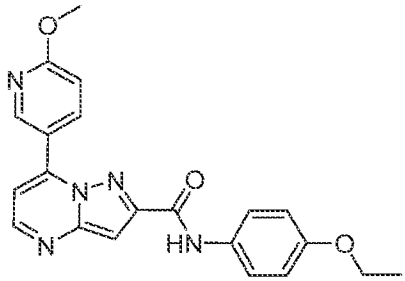
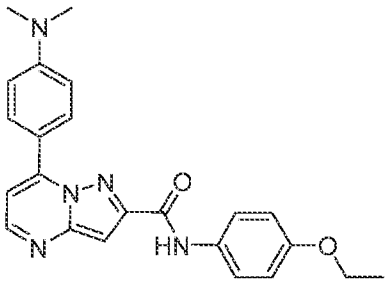
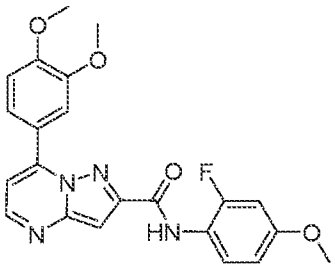
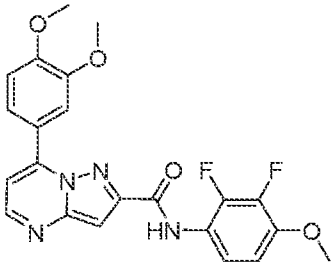
291		N-(3,5-bis(trifluoromethyl)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
292		7-(3,4-dimethoxyphenyl)-N-(4-(hydroxymethyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
293		7-(3,4-difluorophenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
294		7-(4-methoxy-3-nitrophenyl)-N-(5-morpholinopyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
295		N-(4-ethoxyphenyl)-7-(4-methoxy-3-nitrophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
296		N-(4-ethoxyphenyl)-7-(2-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

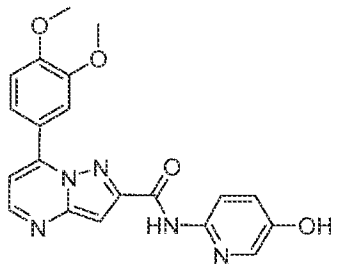
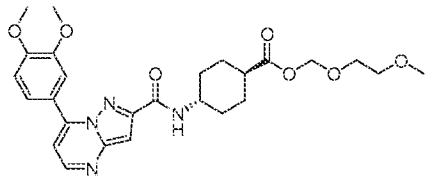
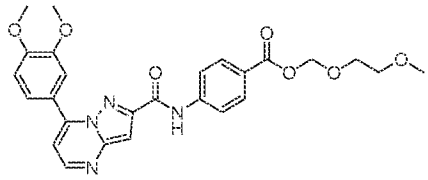
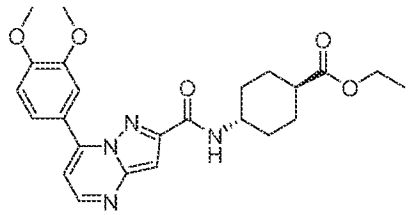
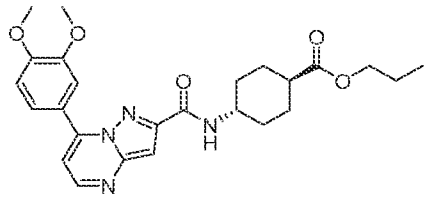
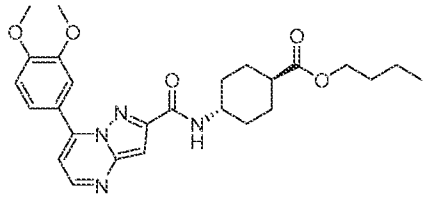
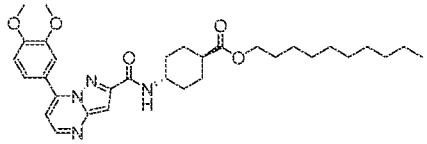
297		7-(2-fluoro-4-methoxyphenyl)-N-(5-morpholinopyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
298		7-(3-chloro-4-(trifluoromethoxy)phenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
299		7-(3-chloro-4-(trifluoromethoxy)phenyl)-N-(5-morpholinopyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
301		N-(4-ethoxyphenyl)-7-(m-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
302		N-(4-ethoxyphenyl)-7-(4-fluoro-3-methylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
303		N-(4-ethoxyphenyl)-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

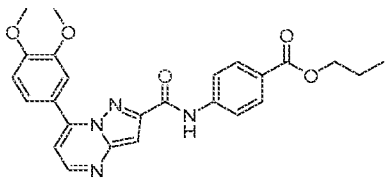
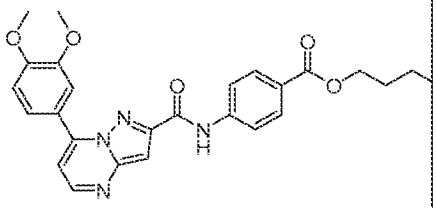
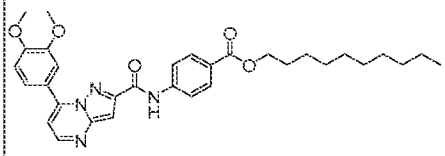
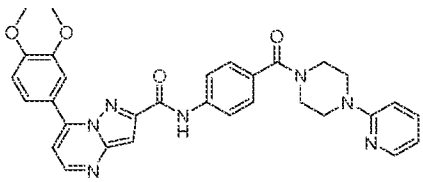
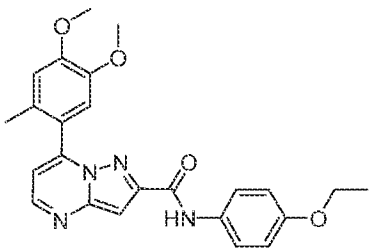
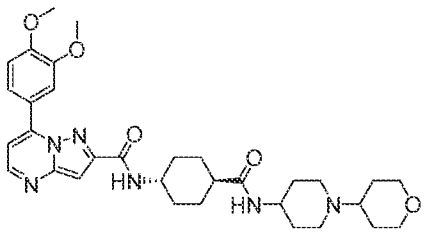
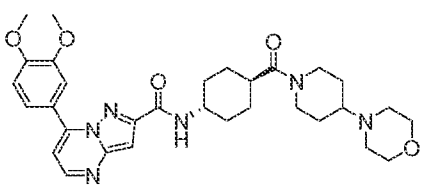
304		7-(4-chloro-2-fluorophenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
306		N-(5-morpholinopyridin-2-yl)-7-(m-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
307		N-(4-ethoxyphenyl)-7-(4-fluoro-3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
308		N-(4-ethoxyphenyl)-7-(3-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
309		7-(3,4-dimethoxyphenyl)-N-(1-methyl-1H-indol-5-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
311		7-(3,4-dimethoxyphenyl)-N-(2-fluoro-4-morpholinophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

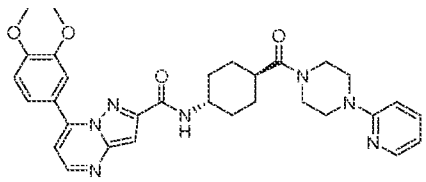
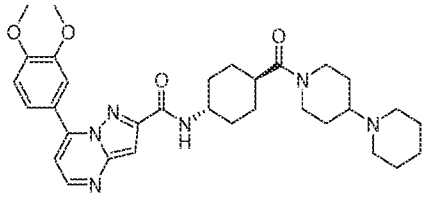
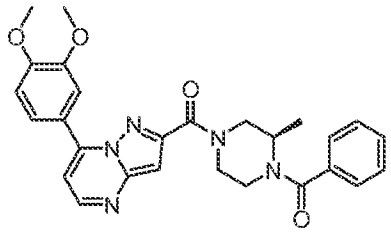
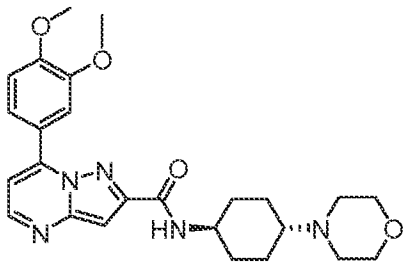
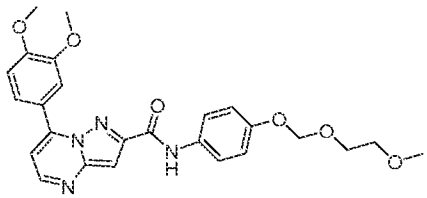
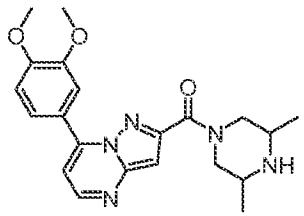
312		7-(3,4-dimethoxyphenyl)-N-(5-(dimethylamino)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
313		7-(2,3-dihydrobenzofuran-5-yl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
314		7-(3,4-dimethoxyphenyl)-N-(5-ethoxypyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
315		7-(3,5-dimethoxyphenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
316		7-(3-chloro-4-fluorophenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

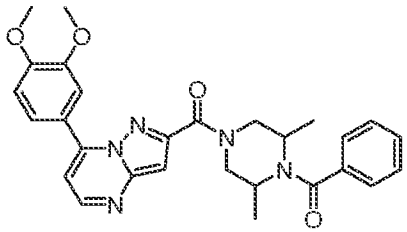
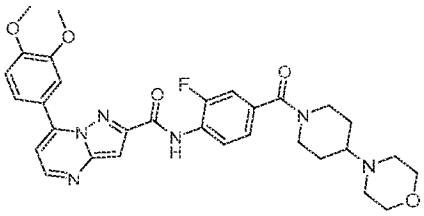
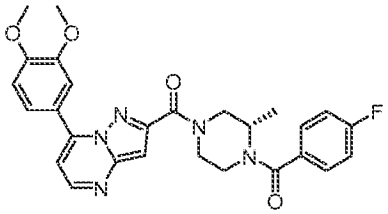
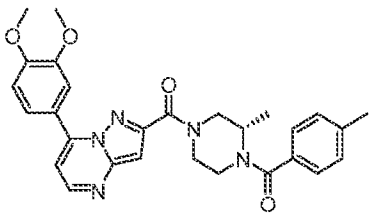
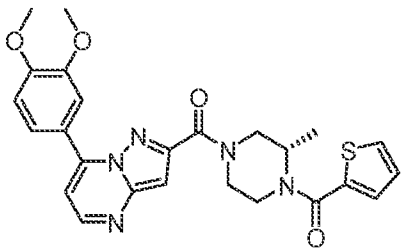
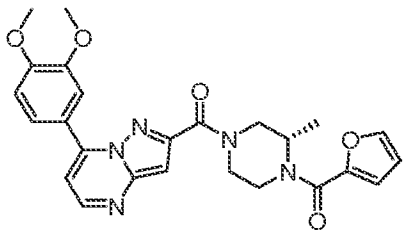
317		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(2-methoxybenzoyl)-3-methylpiperazin-1-yl)methanone
318		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(3-methoxybenzoyl)-3-methylpiperazin-1-yl)methanone
319		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(4-methoxybenzoyl)-3-methylpiperazin-1-yl)methanone
320		7-(3,4-dimethoxyphenyl)-N-(4-morpholinobicyclo[2.2.2]octan-1-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
321		tert-butyl (R)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2-methylpiperazine-1-carboxylate

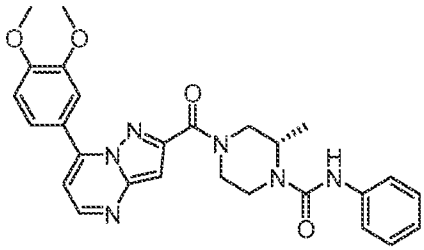
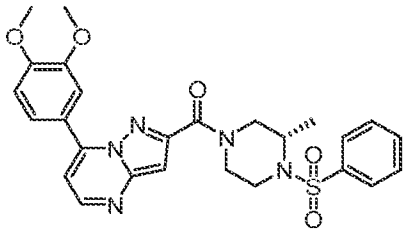
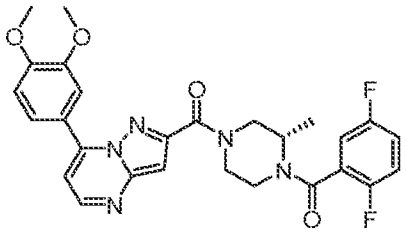
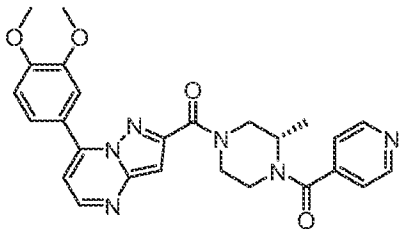
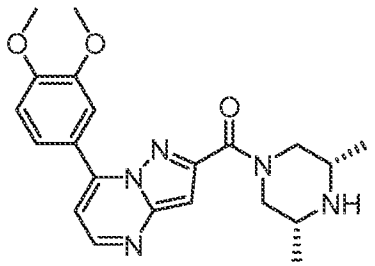
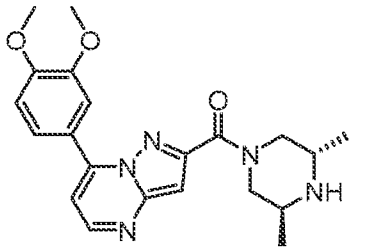
322		(R)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methylpiperazin-1-yl)methanone
323		N-(4-ethoxyphenyl)-7-(6-methoxypyridin-3-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
324		7-(4-(dimethylamino)phenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
325		7-(3,4-dimethoxyphenyl)-N-(2-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
326		N-(2,3-difluoro-4-methoxyphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

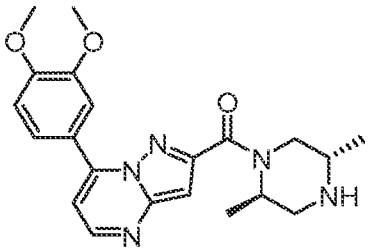
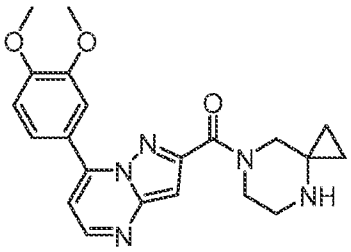
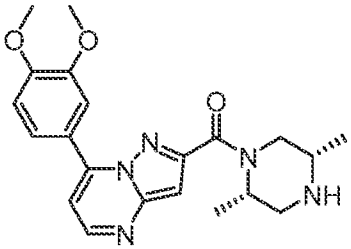
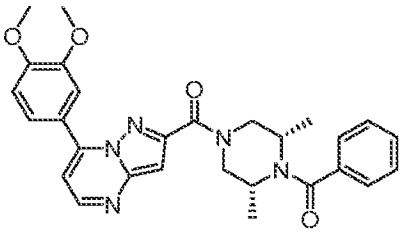
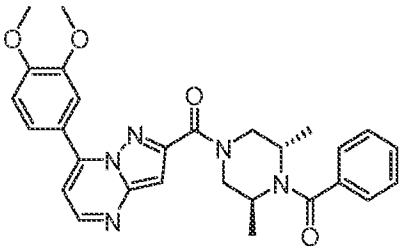
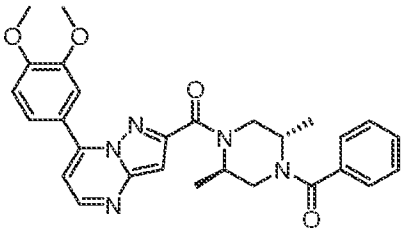
327		7-(3,4-dimethoxyphenyl)-N-(5-hydroxypyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
328		(2-methoxyethoxy)methyl (1R,4R)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
329		(2-methoxyethoxy)methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
330		ethyl (1R,4R)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
331		propyl (1R,4R)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
332		butyl (1r,4r)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate
333		decyl (1r,4r)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate

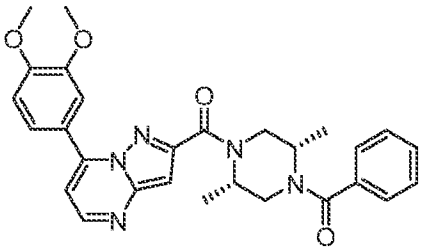
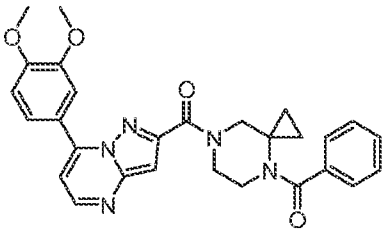
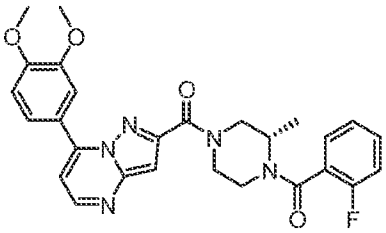
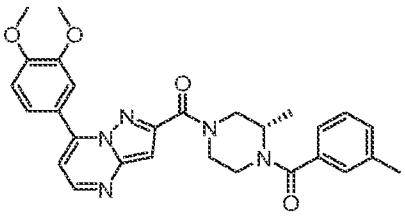
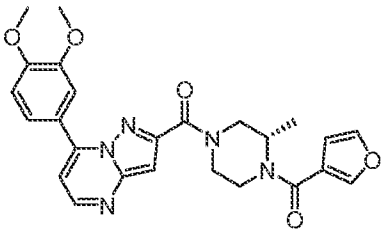
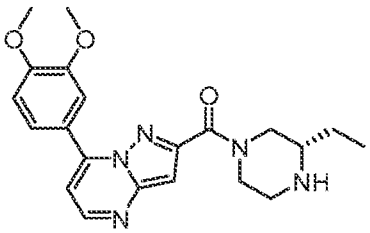
335		propyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
336		butyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
337		decyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
338		7-(3,4-dimethoxyphenyl)-N-(4-(4-(pyridin-2-yl)piperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
339		7-(4,5-dimethoxy-2-methylphenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
340		7-(3,4-dimethoxyphenyl)-N-((1R,4R)-4-((1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)carbamoyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
341		7-(3,4-dimethoxyphenyl)-N-((1R,4R)-4-(4-morpholinopiperidine-1-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

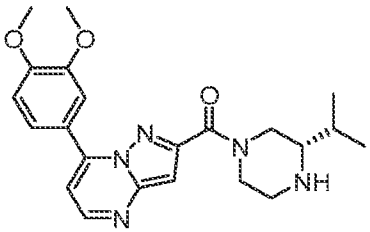
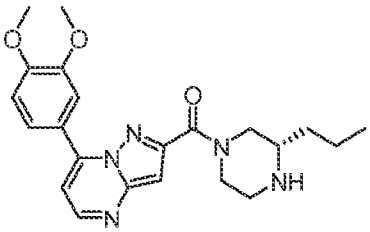
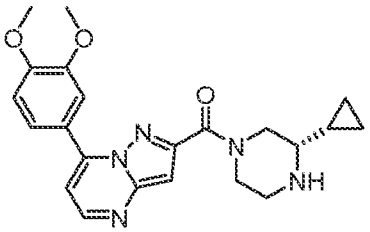
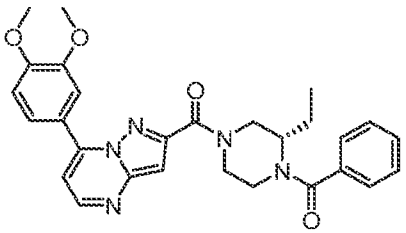
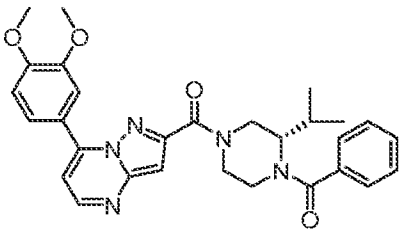
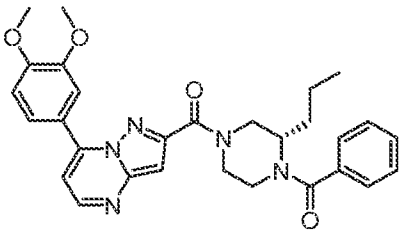
342		7-(3,4-dimethoxyphenyl)-N-((1R,4R)-4-(4-(pyridin-2-yl)piperazine-1-carbonyl)cyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
343		N-((1R,4R)-4-([1,4'-bipiperidine]-1'-carbonyl)cyclohexyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
344		(R)-(4-benzoyl-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
345		7-(3,4-dimethoxyphenyl)-N-((1R,4R)-4-morpholinocyclohexyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
346		7-(3,4-dimethoxyphenyl)-N-(4-((2-methoxyethoxy)methoxy)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
347		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3,5-dimethylpiperazin-1-yl)methanone

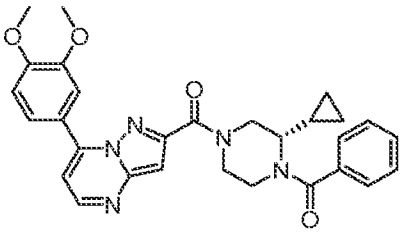
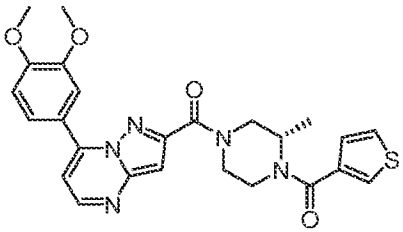
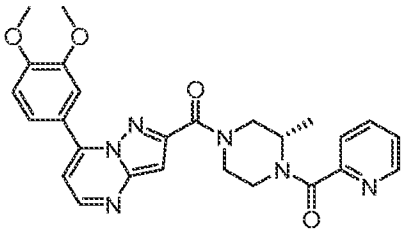
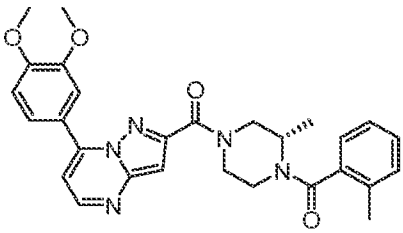
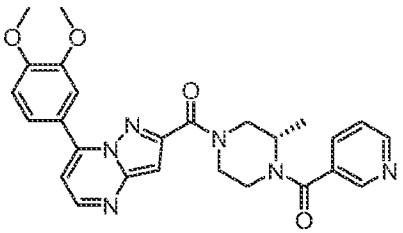
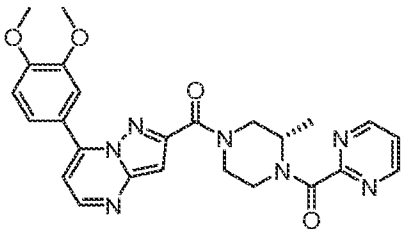
348		(4-benzoyl-3,5-dimethylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
349		7-(3,4-dimethoxyphenyl)-N-(2-fluoro-4-(4-morpholinopiperidine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
350		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(4-fluorobenzoyl)-3-methylpiperazin-1-yl)methanone
351		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(4-methylbenzoyl)piperazin-1-yl)methanone
352		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methanone
353		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)methanone

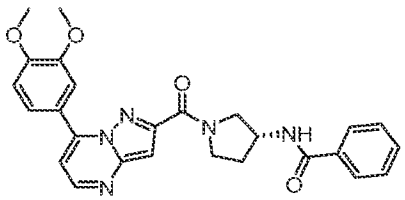
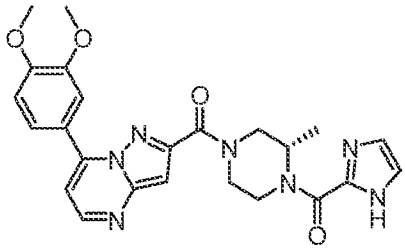
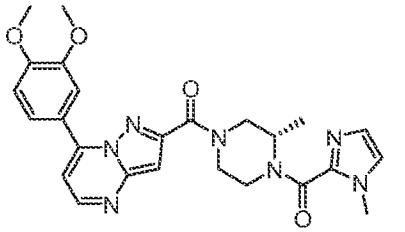
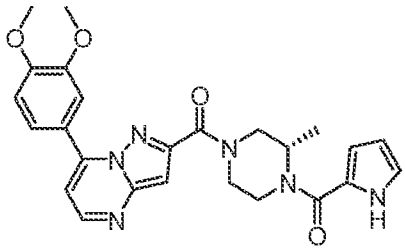
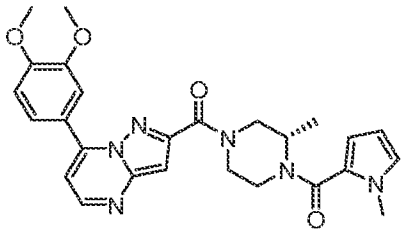
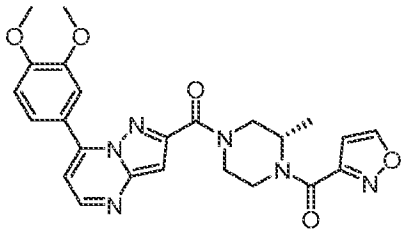
354		(S)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2-methyl-N-phenylpiperazine-1-carboxamide
355		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(phenylsulfonyl)piperazin-1-yl)methanone
356		(S)-(4-(2,5-difluorobenzoyl)-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
357		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-isonicotinoyl-3-methylpiperazin-1-yl)methanone
358		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)((3R,5S)-3,5-dimethylpiperazin-1-yl)methanone
359		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)((3S,5S)-3,5-dimethylpiperazin-1-yl)methanone

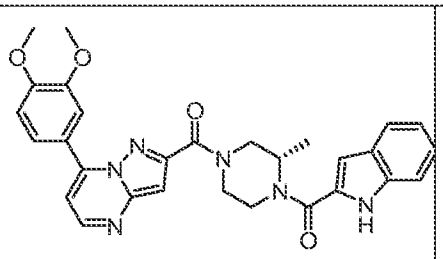
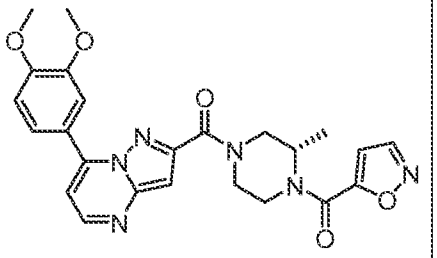
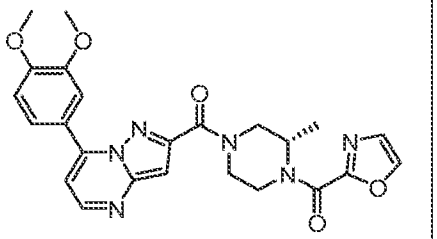
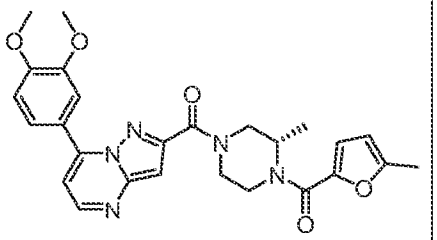
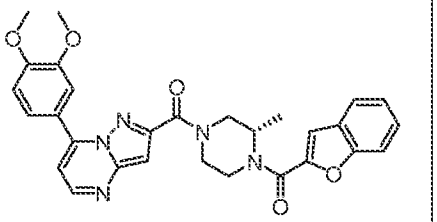
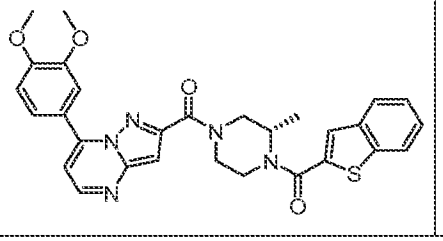
360		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)((2R,5S)-2,5-dimethylpiperazin-1-yl)methanone
361		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4,7-diazaspiro[2.5]octan-7-yl)methanone
362		(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)((2S,5S)-2,5-dimethylpiperazin-1-yl)methanone
363		((3R,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
364		((3S,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
365		((2R,5S)-4-benzoyl-2,5-dimethylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone

366		((2S,5S)-4-benzoyl-2,5-dimethylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
367		(4-benzoyl-4,7-diazaspiro[2.5]octan-7-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
368		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(2-fluorobenzoyl)-3-methylpiperazin-1-yl)methanone
369		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(3-methylbenzoyl)piperazin-1-yl)methanone
370		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)methanone
371		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-ethylpiperazin-1-yl)methanone

372		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-isopropylpiperazin-1-yl)methanone
373		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-propylpiperazin-1-yl)methanone
374		(S)-(3-cyclopropylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
375		(S)-(4-benzoyl-3-ethylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
376		(S)-(4-benzoyl-3-isopropylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
377		(S)-(4-benzoyl-3-propylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone

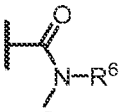
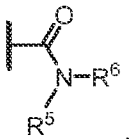
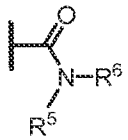
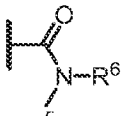
378		(S)-(4-benzoyl-3-cyclopropylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
379		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(thiophene-3-carbonyl)piperazin-1-yl)methanone
380		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-picolinoylpiperazin-1-yl)methanone
381		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(2-methylbenzoyl)piperazin-1-yl)methanone
382		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-nicotinoylpiperazin-1-yl)methanone
383		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(pyrimidine-2-carbonyl)piperazin-1-yl)methanone

384		(R)-N-(1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)pyrrolidin-3-yl)benzamide
385		(S)-(4-(1H-imidazole-2-carbonyl)-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
386		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(1-methyl-1H-imidazole-2-carbonyl)piperazin-1-yl)methanone
387		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(1H-pyrrole-2-carbonyl)piperazin-1-yl)methanone
388		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(1-methyl-1H-pyrrole-2-carbonyl)piperazin-1-yl)methanone
389		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(isoxazole-3-carbonyl)-3-methylpiperazin-1-yl)methanone

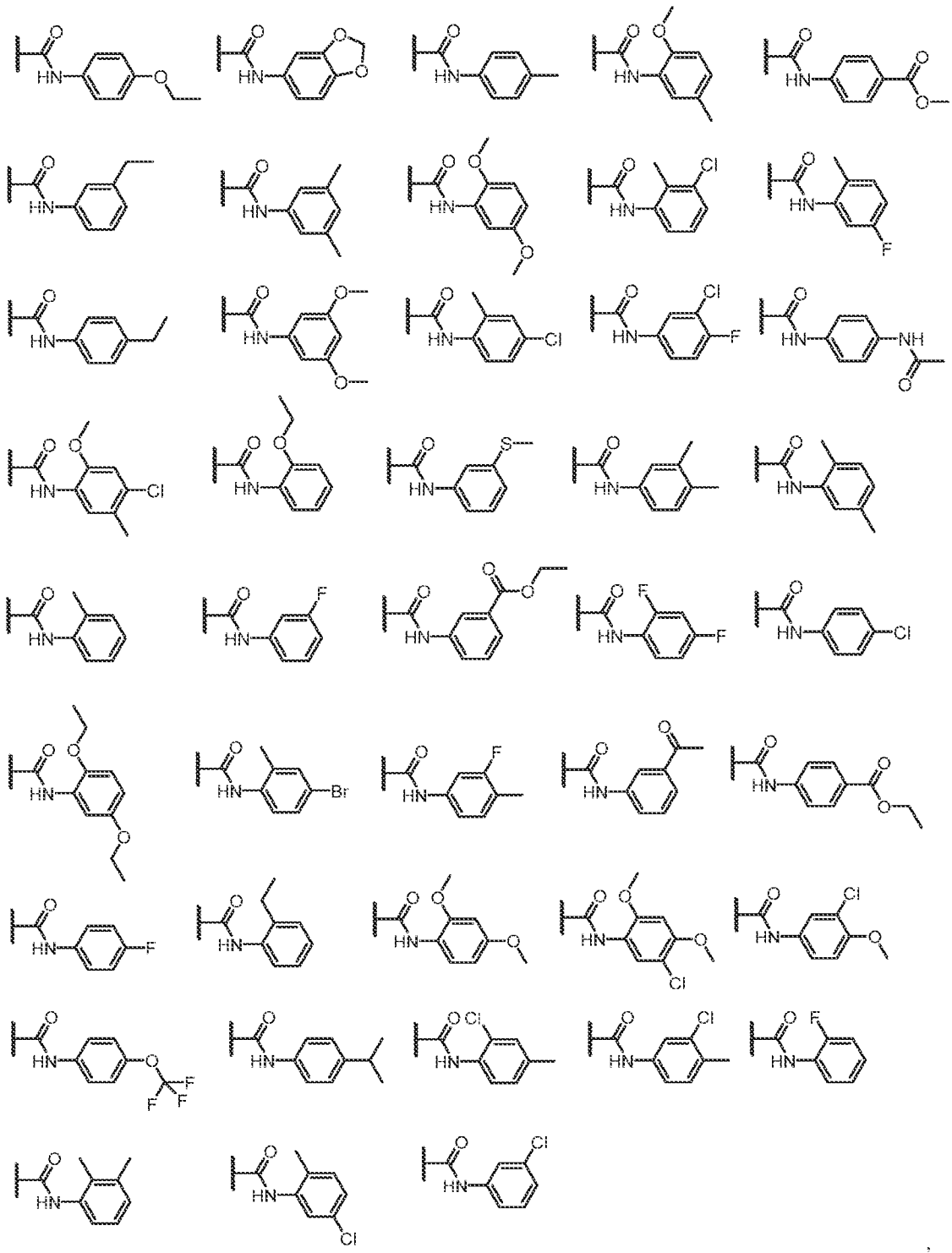
390		(S)-(4-(1H-indole-2-carbonyl)-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
391		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(isoxazole-5-carbonyl)-3-methylpiperazin-1-yl)methanone
392		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(oxazole-2-carbonyl)piperazin-1-yl)methanone
393		(S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methyl-4-(5-methylfuran-2-carbonyl)piperazin-1-yl)methanone
394		(S)-(4-(benzofuran-2-carbonyl)-3-methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone
395		(S)-benzo[b]thiophen-2-yl(4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2-methylpiperazin-1-yl)methanone

[00138] In some embodiments of formula (Ia), the compound is of Table 2, or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof.

[00139] In some embodiments of formula (Ia), the compound is NOT a compound of Table 2, or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof.

[00140] In some embodiments of formula (Ia), when R^1 and R^9 are H, R^4 is  , R^5 is H, and R^6 is substituted aryl; then R^2 is not 4-fluoro-phenyl. In some embodiments of formula (Ia), when R^1 and R^9 are H, R^4 is  , R^5 is H, and R^6 is substituted aryl; then R^2 is not *para*-toluene. In some embodiments of formula (Ia), when R^1 and R^9 are H, R^4 is  , R^5 is H, and R^6 is substituted aryl; then R^2 is not 3,5-dichloro-phenyl. In some embodiments of formula (Ia), when R^1 and R^9 are H, R^4 is  , R^5 is H, and R^6 is optionally substituted aryl; then R^2 is not phenyl.

[00141] In some embodiments of formula (Ia), when R^1 and R^9 are H, and R^4 is any one of the following:



then R^2 is not 3,4-dimethoxy-phenyl.

Table 2: Exemplary Compounds	
Cmpd	**Name**
3	7-(3,4-dimethoxyphenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
5	7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid
11	methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
267	7-(3,4-dimethoxyphenyl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
300	N-(4-ethoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
305	methyl 4-(7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
310	N-(benzo[d][1,3]dioxol-5-yl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
334	ethyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
396	7-(3,4-dimethoxyphenyl)-N-(p-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
397	N-(4-chlorophenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
398	7-(3,4-dimethoxyphenyl)-N-(4-ethylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
399	7-(3,4-dimethoxyphenyl)-N-(4-(trifluoromethoxy)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
400	7-(3,4-dimethoxyphenyl)-N-(4-isopropylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
401	N-(2-chloro-4-methylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
402	N-(3-chloro-4-methylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
403	N-(3-chloro-4-methoxyphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
404	7-(3,4-dimethoxyphenyl)-N-(3-fluoro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
405	7-(3,4-dimethoxyphenyl)-N-(3,4-dimethylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
406	N-(3-chloro-4-fluorophenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
407	N-(4-acetamidophenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

408	N-(4-chloro-2-methylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
409	N-(2,4-difluorophenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
410	N-(4-bromo-2-methylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
411	N-(2,4-dimethoxyphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
412	N-(5-chloro-2,4-dimethoxyphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
413	N-(4-chloro-2-methoxy-5-methylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
414	7-(3,4-dimethoxyphenyl)-N-(2-methoxy-5-methylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
415	7-(3,4-dimethoxyphenyl)-N-(2,5-dimethylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
416	N-(2,5-diethoxyphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
417	N-(5-chloro-2-methylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
418	N-(2,5-dimethoxyphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
419	7-(3,4-dimethoxyphenyl)-N-(5-fluoro-2-methylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
420	7-(3,4-dimethoxyphenyl)-N-(2-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
421	7-(3,4-dimethoxyphenyl)-N-(o-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
422	7-(3,4-dimethoxyphenyl)-N-(2-ethylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
423	7-(3,4-dimethoxyphenyl)-N-(2-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
424	7-(3,4-dimethoxyphenyl)-N-(2,3-dimethylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
425	N-(3-chloro-2-methylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
426	N-(3-chlorophenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
427	N-(4-(4-chloro-1H-pyrazol-1-yl)phenyl)-7-(3,5-dichlorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

428	7-(3,4-dimethoxyphenyl)-N-(3-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
429	7-(3,4-dimethoxyphenyl)-N-(3-ethylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
430	7-(3,4-dimethoxyphenyl)-N-(3-(methylthio)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
431	N-(3-acetylphenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
432	ethyl 3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate
433	7-(3,4-dimethoxyphenyl)-N-(3,5-dimethylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
434	7-(3,4-dimethoxyphenyl)-N-(3,5-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
435	N-(2,5-dimethoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
436	N-(2,4-dimethoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
437	N-(4-methoxy-2-methylphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
438	N-(4-fluoro-2-methylphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
439	N-(2,4-difluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
440	N-(3-methoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
441	N-(2-methoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
442	N-(2-ethoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
443	N-(4-methoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
445	N-(4-fluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
446	N-(2-fluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
447	N-(3-fluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
448	N-(3-fluoro-4-methylphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
449	N-(3,4-difluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
450	N-(2-ethoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
451	N-(3-chloro-4-methoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
452	N-(3-chloro-4-fluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
453	N-(5-chloro-2-methoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
454	N-(2-methoxy-5-methylphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
455	N-(5-fluoro-2-methylphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide

456	N-(2-fluoro-5-methylphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
457	N-(2,5-difluorophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
458	N-(4-acetamidophenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
459	7-phenyl-N-(4-(trifluoromethoxy)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
460	indolin-1-yl(7-phenylpyrazolo[1,5-a]pyrimidin-2-yl)methanone
461	7-(4-fluorophenyl)-N-(3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
462	7-(4-fluorophenyl)-N-(2-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
463	N-(2-ethoxyphenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
464	N-(3,4-dimethoxyphenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
465	7-(4-fluorophenyl)-N-(4-methoxy-2-methylphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
466	N-(2,5-difluorophenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
467	N-(4-acetylphenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
468	N-(2,4-difluorophenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
469	N-(5-fluoro-2-methylphenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
470	N-(4-fluoro-2-methylphenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
471	N-(4-ethoxyphenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
472	N-(4-(dimethylamino)phenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
473	N-(4-acetamidophenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
474	N-(4-carbamoylphenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
475	N-(2-fluorophenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
476	7-(4-fluorophenyl)-N-(o-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
474	7-(4-fluorophenyl)-N-(m-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
478	7-(4-fluorophenyl)-N-phenylpyrazolo[1,5-a]pyrimidine-2-carboxamide
479	N-(3-acetylphenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
480	N-(4-fluoro-3-nitrophenyl)-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
481	(7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(indolin-1-yl)methanone
482	N-mesityl-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

483	N-(4-methoxy-2-methylphenyl)-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
484	N-(2-chloro-6-methylphenyl)-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide
485	N-(4-(4-chloro-1H-pyrazol-1-yl)phenyl)-7-(3,5-dichlorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

[00142] It is understood that all variations of salts, solvates, hydrates, prodrugs and/or stereoisomers of the compounds described herein are meant to be encompassed by the present disclosure.

5.1.1. Isotopically Labelled Analogs

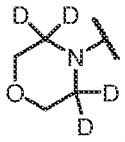
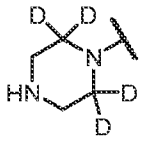
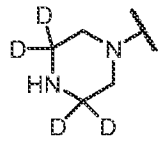
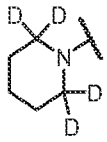
[00143] The present disclosure also encompasses isotopically-labeled compounds which are identical to those compounds as described herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature ("isotopologues"). The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more atoms that constituted such compounds. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H ("D"), ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. For example, a compound described herein can have one or more H atoms replaced with deuterium.

[00144] Generally, reference to or depiction of a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Compounds comprising radioisotopes such as tritium, ^{14}C, ^{32}P and ^{35}S are thus within the scope of the present technology. Procedures for inserting such labels into the compounds of the present technology will be readily apparent to those skilled in the art based on the disclosure herein.

[00145] Unless otherwise stated, compounds described herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C- enriched carbon are within the scope of the present disclosure.

[00146] In some embodiments, certain isotopically-labeled compounds, such as those labeled with ^{3}H and ^{14}C, can be useful in compound and/or substrate tissue distribution assays. Tritiated (^{3}H) and carbon-14 (^{14}C) isotopes can be particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium can afford certain therapeutic advantages resulting from greater metabolic stability, such as increased in vivo half-life or reduced dosage requirements, and hence can be preferred in some circumstances. Isotopically-labeled compounds can generally be prepared by following procedures analogous to those disclosed herein, for example, in

the Examples section, by substituting an isotopically-labeled reagent for a non-isotopically-labeled reagent.

[00147] In some embodiments, the compounds disclosed in the present disclosure are deuterated analogs of any of the compounds, or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, as described herein. A deuterated analog of a compound of formula (Ia)-(Ie) is a compound where one or more hydrogen atoms are substituted with a deuterium. In some embodiments, the deuterated analog is a compound of formula (Ia) that includes a deuterated R^x group, e.g., R^1- R^9 group. In some embodiments of a deuterated analog of a compound of formula (Ia), wherein the optional substituent is an optionally substituted heterocycloalkyl including at least one deuterium atom (e.g.  ,  ,  , and ).

[00148] Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] 2000, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, 1989, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., 1981, 64(1-2), 9-32.

[00149] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

5.1.2. Fluorinated Analogs

[00150] In some embodiments, the compounds disclosed in the present disclosure are fluorinated analogs of any of the compounds, or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, as described herein. A fluorinated analog of a compound of formula (Ia)-(Ie) is a compound where one or more hydrogen atoms or substituents are substituted with a fluorine atom. In some embodiments, the fluorinated analog is a compound of formula (Ia)-(Ie) that includes a fluorinated R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{31}, R^{32} group, or other substituent R group. In some embodiments of a fluorinated analog of a compound of formula (Ia)-(Ie), the hydrogen atom of an aliphatic or an aromatic C-H bond is replaced by a fluorine atom. In some embodiments of a fluorinated analog of a compound of formula (Ia)-(Ie), at least one hydrogen of an optionally substituted aryl or an optionally substituted heteroaryl is replaced by a fluorine atom. In some embodiments of a fluorinated analog of a

compound of formula (Ia)-(Ie), a hydroxyl substituent (-OH) or an amino substituent (-NH_2) is replaced by a fluorine atom.

5.1.3. Isomers

[00151] The term "compound", as used herein, is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

[00152] The compounds herein described may have asymmetric centers, geometric centers (e.g., double bond), or both. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. In some embodiments, the compounds described herein have one or more chiral centers. It is understood that if an absolute stereochemistry is not expressly indicated, then each chiral center may independently be of the R-configuration or the S-configuration or a mixture thereof. Thus, compounds described herein include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Racemic mixtures of R-enantiomer and S-enantiomer, and enantio-enriched stereomeric mixtures comprising of R- and S-enantiomers, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these stereoisomers are all within the scope of the present technology.

[00153] Compounds of the present disclosure containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms, by synthesis from optically active starting materials, or through use of chiral auxiliaries.

[00154] Geometric isomers, resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a cycloalkyl or heterocyclic ring, can also exist in the compounds of the present disclosure. Geometric isomers of olefins, C=N double bonds, or other types of double bonds may be present in the compounds described herein, and all such stable isomers are included in the present disclosure. Specifically, cis and trans geometric isomers of the compounds of the present disclosure may also exist and may be isolated as a mixture of isomers or as separated isomeric forms.

[00155] Compounds of the present disclosure also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Examples prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H-

isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

5.1.4. Salts and other forms

[00156] In some embodiments, the compounds described herein are present in a salt form. In some embodiments, the compounds are provided in the form of pharmaceutically acceptable salts.

[00157] Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that can be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including but not limited to, chloride.

[00158] Compounds containing an amine functional group or a nitrogen-containing heteroaryl group may be basic in nature and may react with a variety of inorganic and organic acids to form the corresponding salts. The compounds could be used in the form of a pharmaceutically acceptable salt derived from inorganic acid or organic acid. In some embodiments, the pharmaceutically acceptable salt could be a salt derived from hydrochloric acid (i.e., a hydrochloride salt of a compound as described herein), or the like.

[00159] The pharmaceutically acceptable salts of the compounds of this disclosure could be produced by dissolving the compound in a water-miscible organic solvent, such as acetone, methanol, ethanol, or acetonitrile, and so on, and adding excessive amount of organic acid or inorganic acid aqueous solution and precipitating or crystalizing. Then, it is possible to obtain additional salt by evaporating the solvent or excessive acid from this mixture and then drying it or by produce salt by filtering extracted salt.

[00160] Other examples of salts include anions of the compounds of the present disclosure compounded with a suitable cation. For therapeutic use, salts of the compounds of the present disclosure can be pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[00161] Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts.

[00162] Compounds that include a basic or acidic moiety can also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure can contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[00163] The compounds described herein can be present in various forms including crystalline, powder and amorphous forms of those compounds, pharmaceutically acceptable salts, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[00164] The compounds described herein may exist as solvates, especially hydrates, and unless otherwise specified, all such solvates and hydrates are intended. Hydrates may form during manufacture of the compounds or compositions comprising the compounds, or hydrates may form over time due to the hygroscopic nature of the compounds. Compounds of the present technology may exist as organic solvates as well, including DMF, ether, and alcohol solvates, among others. The identification and preparation of any particular solvate is within the skill of the ordinary artisan of synthetic organic or medicinal chemistry.

[00165] In some embodiments, the compounds described herein are present in a solvate form. In some embodiments, the compounds described herein are present in a hydrate form when the solvent component of the solvate is water.

5.1.5. Prodrugs

[00166] Aspects of this disclosure include prodrug forms of any of the compounds described herein. Any convenient prodrug forms of the subject compounds can be prepared, for example, according to the strategies and methods described by Rautio *et al.* ("Prodrugs: design and clinical applications", Nature Reviews Drug Discovery 7, 255-270 (February 2008)).

[00167] The term "prodrug" refers to an agent which is converted into a biologically active drug *in vivo* by some physiological or chemical process. In some embodiments, a prodrug is converted to the desired drug form, when subjected to a biological system at physiological pH. In some embodiments, a prodrug is enzymatically converted to the desired drug form, when subjected to a biological system.

[00168] Prodrugs forms of any of the compounds described herein can be useful, for example, to provide particular therapeutic benefits as a consequence of an extension of the half-life of the resulting compound in the body, or a reduction in the active dose required.

[00169] Pro-drugs can also be useful in some situations, as they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The pro-drug may also have improved solubility in pharmacological compositions over the parent drug.

[00170] Prodrug forms or derivatives of a compound of this disclosure generally include a promoiety substituent at a suitable labile site of the compound. The promoiety refers to the group that can be removed by enzymatic or chemical reactions, when a prodrug is converted to the drug *in vivo*.

[00171] In some embodiments, the promoiety is a group (e.g., a optionally substituted C1-6 alkanoyl, or an optionally substituted C1-6 alkyl) attached via an ester linkage to a hydroxyl group or a carboxylic acid group of the compound or drug.

5.2. Compound Synthesis

[00172] Compounds of the present disclosure may be synthesized according to standard methods known in the art [see, e.g. Morrison and Boyd in "Organic Chemistry", 6th edition, Prentice Hall (1992)]. Some compounds and/or intermediates of the present disclosure may be commercially available, known in the literature, or readily obtainable by those skilled in the art using standard procedures. Some compounds of the present disclosure may be synthesized using schemes, examples, or intermediates described herein. Where the synthesis of a compound, intermediate or variant thereof is not fully described, those skilled in the art can recognize that the reaction time, number of equivalents of reagents and/or temperature may be modified from reactions described herein to prepare compounds presented or intermediates or variants thereof and that different work-up and/or purification techniques may be necessary or desirable to prepare such compounds, intermediates, or variants.

[00173] Synthesized compounds may be validated for proper structure by methods known to those skilled in the art, for example by nuclear magnetic resonance (NMR) spectroscopy and/or mass spectrometry.

[00174] In various embodiments, the compound as described herein is represented by the structure of one of the compounds in Table 3A-3B of Example 2 below. The present disclosure is meant to encompass a compound of any one of Tables 1-2, or a salt, a single stereoisomer, a mixture of stereoisomers and/or an isotopically labelled form thereof.

5.3. Pharmaceutical Compositions

[00175] Compounds of the present disclosure may be included in a pharmaceutical composition that includes one or more compounds and at least one excipient (e.g., a pharmaceutically acceptable excipient). Such compositions may include a CFTR modulator and/or PDE4 inhibitor compound of formula (Ia)-(Ie), or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, e.g., as described herein.

[00176] The compounds described herein can find use in pharmaceutical compositions for administration to a subject in need thereof in a variety of therapeutic applications where modulation of CFTR, or inhibition of PDE4, is desirable.

[00177] Accordingly, another aspect of the present disclosure provides pharmaceutical compositions comprising at least one compound described herein, a pharmaceutically acceptable salt thereof, or a

prodrug, a solvate, a hydrate, or a stereoisomer thereof, and at least one pharmaceutically acceptable excipient.

[00178] The phrase "**pharmaceutically acceptable excipient**," refers any ingredient other than the compounds of this disclosure described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: anti-adherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, dispensing, or dispersing agents, sweeteners, and waters of hydration. In some embodiments, the pharmaceutical composition comprises a compound as described herein, a pharmaceutically acceptable salt thereof, or a prodrug, a solvate, a hydrate, or a stereoisomer thereof in a therapeutically effective amount.

5.3.1.1. Ophthalmic Compositions

[00179] In some embodiments, the pharmaceutical compositions are formulated for ophthalmic administration. In some embodiments, the pharmaceutical compositions are ophthalmic compositions formulated for topical administration, e.g., to the eye of a human subject. In some embodiments of the ophthalmic composition, the composition is an aqueous solution.

[00180] Thus, the present disclosure provides an ophthalmic composition including a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof as described herein, and a physiologically compatible ophthalmic vehicle.

5.3.1.2. Other Compositions

[00181] The pharmaceutical compositions of this disclosure may be formulated according to any convenient methods, and may also be prepared in various forms for oral administration such as tablets, pills, powders, nanoparticles, capsules, syrups, suspensions, emulsions and microemulsions, or in forms for non-oral administration such as preparations for intramuscular, intravenous, transdermal or subcutaneous administration.

[00182] In a specific example, the pharmaceutical composition could contain a pharmaceutically allowed carrier, excipient, or additive. The pharmaceutical composition could be produced as medicine in the conventional method, and could be produced as various oral medicine such as tablet, pill, powder, capsule, syrup, emulsion, micro-emulsion, and so on, or could be produced as non-oral medicine such as muscular injection, vascular injection, or subcutaneous injection.

[00183] If the pharmaceutical composition is produced in the form of an oral medicine, examples of the used additive or carrier could include cellulose, silicic calcium, corn starch, lactose, sucrose,

dextrose, phosphoric acid calcium, stearic acid, stearic acid magnesium, stearic acid calcium, gelatin, talc, surfactant, suspension, emulsifying agent, diluting agent, and so on. If the pharmaceutical composition of this disclosure is produced in the form of an injection, the additives or carrier could include water, saline water, glucose aqueous solution, similar sugar-soluble solution, alcohol, glycol, ether (e.g., polyethylene glycol 400), oil, fatty acid, fatty acid ester, glyceride, surfactant, suspension, emulsifying agent, and so on.

[00184] In some embodiments, the pharmaceutical compositions are formulated for parenteral administration to a subject in need thereof. In some parenteral embodiments, the pharmaceutical compositions are formulated for intravenous administration to a subject in need thereof. In some parenteral embodiments, the pharmaceutical compositions are formulated for subcutaneous administration to a subject in need thereof. In some parenteral embodiments, the pharmaceutical compositions are formulated for transdermal administration to a subject in need thereof.

5.4. Methods of Modulating CFTR

[00185] Aspects of the present disclosure include methods of modulating CFTR with compounds as described herein. Such methods may include methods of modulating CFTR in biological systems by contacting such systems with CFTR modulator compounds (e.g., CFTR modulator compounds having structures according to any of those of Table 1 or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof). Biological systems may include, but are not limited to, cells, tissues, organs, bodily fluids, organisms, non-mammalian subjects, and mammalian subjects (e.g., humans). A method of contacting biological systems with CFTR modulator compounds may be performed by administering the compounds to subjects.

[00186] The term "modulator" refers to a compound or composition that increases the level of a target or the function of a target, which may be, but is not limited to, CFTR. In some embodiments, the modulator compound can agonize or activate a target, such as CFTR, and increase the level of the target or the function of the target. In this respect, the method of modulating CFTR comprises a method of activating CFTR or the function of CFTR.

[00187] In some embodiments, the CFTR modulator compounds described herein are CFTR activator compounds that are capable of activating CFTR proteins and increasing the level of the function of the CFTR proteins. In another embodiment, the CFTR activator compounds described herein are capable of modulating or activating downstream function(s) resulting from CFTR activation.

[00188] In some embodiments, the method of modulating CFTR includes contacting a biological system or sample comprising CFTR with an effective amount of any of the CFTR modulating compounds or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof as described herein, or a pharmaceutical composition including same as described herein to

modulate CFTR. In certain embodiments, the biological system or sample is *in vitro*. In another embodiment, the biological system or sample is *in vivo*.

[00189] The CFTR modulators may modulate the enzymatic activity of CFTR in a sample. For example, yellow fluorescent protein (YFP)-based binding assay, as described in Example 4, can be used to measure CFTR function. Using such assay, the CFTR function is assessed from the time course of cell fluorescence in response to extracellular addition of iodide ions followed by forskolin that results in decrease YFP fluorescence due to CFTR-mediated iodide entry. CFTR activity can also be assessed by the assay described in Example 5. CFTR modulators according to such method may exhibit EC_{50} values for modulation of CFTR function (e.g. as assessed by short-circuit current measurement assay of Example 5) of less than 2000 nM, such as 200 nM or less. Biological systems may include subjects (e.g., human subjects).

[00190] In some embodiments, the present disclosure provides methods of modulating CFTR activity in a subject. In some cases, the percentage of CFTR activity modulated in a subject may be at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least, 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or at least 99.9%. In some embodiments, the CFTR activity is increased, e.g., at least 10% or more, as compared to a baseline level of CFTR activity measured in a sample of the subject.

[00191] In some embodiments, compounds of the present disclosure may be used in assays to assess CFTR modulation activity. Some assays may include diagnostic assays. In some cases, compounds may be included in methods of drug discovery. In some embodiments, methods of the present disclosure include use of CFTR modulating compounds of the present disclosure to assess CFTR modulation by other compounds. Such methods may include conjugating CFTR modulating compounds with one or more detectable labels (e.g., fluorescent dyes) and measuring CFTR dissociation (via detectable label detection) in the presence of the other compounds. The detectable labels may include fluorescent compounds.

5.5. Methods of Inhibiting PDE4

[00192] Aspects of the present disclosure include methods of inhibiting activity of PDE4 in a biological system or sample by contacting with a compound which exhibit PDE4 inhibiting activity, (e.g., PDE4 inhibitor compounds having structures according to any of those of Tables 1-2, or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof). A method of contacting biological systems with CFTR modulator compounds may be performed by administering the compounds to subjects.

[00193] Biological systems may include, but are not limited to, cells, tissues, organs, bodily fluids, organisms, non-mammalian subjects, and mammalian subjects (e.g., humans). In certain

embodiments, the biological system or sample is *in vitro*. In another embodiment, the biological system or sample is *in vivo*. In some instances, the sample is a cellular sample.

[00194] In some embodiments, the present disclosure provides methods of inhibiting PDE4 activity in a subject. In some cases, the percentage of PDE4 activity inhibited in a subject may be at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least, 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or at least 99.9%. In some cases, this level of inhibition and/or maximum inhibition of PDE4 activity may be achieved by from about 1 hour after administration to about 3 hours after administration, from about 2 hours after administration to about 4 hours after administration, from about 3 hours after administration to about 10 hours after administration, from about 5 hours after administration to about 20 hours after administration, or from about 12 hours after administration to about 24 hours after administration. Inhibition of PDE4 activity may continue throughout a period of at least 1 day, of at least 2 days, of at least 3 days, of at least 4 days, of at least 5 days, of at least 6 days, of at least 7 days, of at least 2 weeks, of at least 3 weeks, of at least 4 weeks, of at least 8 weeks, of at least 3 months, of at least 6 months, or at least 1 year. In some cases, this level of inhibition may be achieved through daily administration. Such daily administration may include administration for at least 2 days, for at least 3 days, for at least 4 days, for at least 5 days, for at least 6 days, for at least 7 days, for at least 2 weeks, for at least 3 weeks, for at least 4 weeks, for at least 2 months, for at least 4 months, for at least 6 months, for at least 1 year, or for at least 5 years. In some cases, subjects may be administered compounds or compositions of the present disclosure for the life of such subjects.

5.6. Therapeutic Indications

[00195] Methods of the present disclosure include methods of treating therapeutic indications using compounds and/or compositions disclosed herein. The term "therapeutic indication" refers to any symptom, condition, disorder, or disease that may be alleviated, stabilized, improved, cured, or otherwise addressed by some form of treatment or other therapeutic intervention (e.g., through CFTR modulator or PDE4 inhibitor administration).

5.6.1. CFTR-related indications

[00196] Therapeutic indications associated with CFTR activity and/or dysfunction are referred to herein as "CFTR-related indications." In some embodiments, methods of the present disclosure may include treating CFTR-related indications by administering compounds and/or compositions disclosed herein (e.g., CFTR modulator compounds).

[00197] The terms "treat," "treatment," and the like, refer to relief from or alleviation of pathological processes. In the context of the present disclosure insofar as it relates to any of the other conditions recited herein below, the terms "treat," "treatment," and the like mean to relieve or

alleviate at least one symptom associated with such condition, or to slow or reverse the progression or anticipated progression of such condition.

5.6.1.1. Eye Disease or Disorder

[00198] In another aspect, the present disclosure provides a method of treating an eye disease or disorder, including administering to an eye of a subject a therapeutically effective amount of an ophthalmic composition as described herein. In some embodiments, the subject is human. In some embodiments of the method, the eye disease or disorder is dry eye disease.

[00199] Dry eye disease is a heterogeneous tear film disorder that results in eye discomfort, visual disturbance, and ocular surface pathology. CFTR is a major prosecretory chloride channel at the ocular surface. Activators of ocular surface CFTR activity can lead to increased tear fluid secretion after topical delivery and be useful for treating dry eye disease.

[00200] In some embodiments, the method further includes identifying a subject suffering from dry eye disease. In some embodiments, the method further includes identifying an underlying disease or condition associated with the dry eye disease.

[00201] In some embodiments, the dry eye disease is caused by one or more disease or condition of the group consisting of allergic conjunctivitis, keratoconjunctivitis sicca, age-related dry eye, Stevens-Johnson syndrome, Sjogren's syndrome, ocular cicatrical pemphigoid, corneal injury, infection, Riley-Day syndrome, congenital alacrima, nutritional disorders or deficiencies, pharmacologic side effects, contact lens intolerance, eye stress resulting in glandular and tissue destruction, autoimmune disorders, immuno-deficient disorders, comatose patients who are unable to blink, or environmental exposure to smog, smoke, excessively dry air, airborne particulates, lacrimal deficiency, lacrimal gland duct obstruction, Meibomian oil deficiency, a disorder of eyelid aperture, and ocular surface disease (OSD).

[00202] In some embodiments, the dry eye disease is caused by keratoconjunctivitis sicca, age-related dry eye, Stevens- Johnson syndrome, Sjogren's syndrome, ocular cicatrical pemphigoid, corneal injury, Riley-Day syndrome, or congenital alacrima.

[00203] In some embodiments, the eye disease or disorder treated according to the method of this disclosure is Sjogren's syndrome.

[00204] In some embodiments, the dry eye disease is caused by nutritional disorders or deficiencies, contact lens intolerance, autoimmune disorders, immuno-deficient disorders, comatose patients who are unable to blink, or environmental exposure to smog, smoke, excessively dry air, or airborne particulates.

[00205] In some embodiments, the eye disease or disorder treated according to the method of this disclosure is conjunctivitis. In some embodiments, the conjunctivitis is allergic conjunctivitis or keratoconjunctivitis.

[00206] In some embodiments, the eye disease or disorder is keratitis.

[00207] In some embodiments, one or more symptoms of the dry eye disease are reduced or alleviated in the subject after administration of compounds or compositions disclosed herein.

[00208] In some embodiments, one or more symptoms of the dry eye disease are selected from dryness, burning, ocular itching, photophobia, foreign body sensation, and grittiness.

[00209] In some embodiments, the method further comprises assessing restoration of the natural tear film in the eye after administration.

[00210] In some embodiments, the ophthalmic composition is topically administered to the eye daily or as needed. In certain embodiments, the ophthalmic composition is a solution.

[00211] A tear volume reduction mouse model for dry eye disease can be used to assess the abilities of the compounds of the present disclosure to modulate tear volume in subjects induced with Scopolamine. In some embodiments, the administration of the compounds of the present disclosure can cause significant changes in tear volume as illustrated by Example 6.

5.6.1.2. Other Diseases or Disorders

[00212] Other CFTR-related indications which can be targeted for treatment include, but are not limited to, chronic obstructive pulmonary disease (COPD), asthma, bronchitis, bronchiectasis, celiac disease, constipation, cholestatic liver disease, chronic rhinosinusitis, and hepatic impairment.

[00213] CFTR dysfunction or CFTR hypofunction can be acquired in chronic obstructive pulmonary disease (COPD) and can contribute to other diseases that share clinical features such as asthma, bronchitis and bronchiectasis. The diseases of chronic obstructive pulmonary disease (COPD), and chronic bronchitis are characterized by mucus-congested and inflamed airways. In some embodiments, the compounds of this disclosure can act as anti-inflammatory agents that simultaneously restore or enhance mucociliary clearance through CFTR activation.

[00214] In some embodiments, the CFTR-related indication is COPD.

[00215] In some embodiments, the CFTR-related indication is bronchitis.

[00216] In some embodiments, the CFTR-related indication is bronchiectasis.

[00217] In some embodiments, the CFTR-related indication is asthma.

[00218] In some embodiments, the CFTR-related indication is constipation. Constipation is a common clinical complaint in adults and children that negatively impacts quality of life. In some embodiments, the constipation is opioid-induced constipation, chronic idiopathic constipation or irritable bowel syndrome with constipation predominance. In some embodiments, the CFTR modulating compounds of this disclosure can stimulate intestinal fluid secretion and normalized stool output to treat the constipation.

[00219] In some embodiments, the CFTR-related indication is celiac disease. In celiac disease, an intolerance to dietary gluten/gliadin, antigenic gliadin peptides trigger an HLADQ2/DQ8-restricted adaptive Th1 immune response. CFTR acts as membrane receptor for the gluten/gliadin-derived

peptide (P31–43) which inhibits CFTR in intestinal epithelial cells, causing a local stress response that contributes to the immunopathology of celiac disease. In some embodiments, stimulation of CFTR function with CFTR activating compounds of this disclosure can attenuate the autophagy-inhibition and pro-inflammatory effects of gliadin, and provide for treatment of celiac disease.

[00220] In some embodiments, the CFTR-related indication is cholestatic liver disease.

[00221] In some embodiments, the CFTR-related indication is chronic rhinosinusitis.

[00222] In some embodiments, the CFTR-related indication is hepatic impairment.

5.6.2. PDE4-related indications

[00223] Aspects of the present disclosure include methods of treating therapeutic indications of interest using compounds and/or compositions disclosed herein. Therapeutic indications associated with PDE4 activity and/or dysfunction are referred to herein as "PDE4-related indications." In some embodiments, methods of the present disclosure may include treating PDE4-related indications by administering compounds and/or compositions disclosed herein (e.g., PDE4 inhibitor compounds).

[00224] PDE4 inhibitors are a well characterized class of agent having a variety of anti-inflammatory activities. A human phosphodiesterase4 (PDE4) inhibition assay in host cells can be used to assess the abilities of the compounds of the present disclosure to inhibit target PDE4. In some embodiments, the administration of the compounds of the present disclosure can cause significant changes PDE4 activity as illustrated by Example 7.

[00225] In some embodiments, the PDE4 inhibiting compounds of this disclosure have board anti-inflammatory effects such as the inhibition of TNF-alpha production and several other mediators. PDE4 is a therapeutic target for the treatment of diverse pulmonary, dermatological, and severe neurological diseases.

[00226] In some embodiments of the method, the PDE4-related indication is an inflammatory disease or disorder. In some embodiments, inflammatory disease or disorder is a chronic inflammatory disease or disorder. In some embodiments, inflammatory disease or disorder is an acute inflammatory disease or disorder. In some embodiments of the method, the PDE4-related indication is an autoimmune disease.

[00227] In some embodiments of the method, the PDE4-related indication is an inflammatory lung disease. In some embodiments, the inflammatory lung disease is chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis or an inflammatory airway disease.

[00228] In some embodiments of the method, the PDE4-related indication is an inflammatory skin disease. In some embodiments, the inflammatory skin disease is psoriasis or a psoriatic disorder, such as psoriatic arthritis. In some embodiments, the inflammatory skin disease is atopic dermatitis.

[00229] In some embodiments of the method, the PDE4-related indication is inflammatory bowel disease (IBD).

[00230] In some embodiments of the method, the PDE4-related indication is rheumatoid arthritis.

[00231] In some embodiments of the method, the PDE4-related indication is ankylosing spondylitis.

[00232] In some embodiments of the method, the PDE4-related indication is a neurological disease, such as neuroinflammation.

[00233] In some embodiments of the method, the PDE4-related indication is conjunctivitis. In some embodiments, the conjunctivitis is allergic conjunctivitis or keratoconjunctivitis.

[00234] In some embodiments, the PDE4-related indication is keratitis.

[00235] Accordingly, PDE4-related indications of interest which can be targeted for treatment according to the methods of this disclosure include, but are not limited to, COPD, asthma, inflammatory airway disease, psoriasis, psoriatic disorder, atopic dermatitis, inflammatory bowel disease (IBD), rheumatoid arthritis, ankylosing spondylitis, neuroinflammation, and allergic conjunctivitis.

5.6.3. Administration methods

[00236] In some embodiments, the method includes oral administration of the subject compound or composition. The administration dose may be administrated orally or non-orally depending on the purpose, in an amount effective at prevention or therapy in the individual or patient in question. When administering orally, the compound may be administered so that 0.01 to 1000mg, more specifically 0.1 to 300mg of the active agent is administered per 1kg body weight, and when administering non-orally, the compound may be administered so that 0.01 to 100mg, more specifically 0.1 to 50mg of the active ingredient is administered per 1kg body weight. The dose may be administered at one time or over multiple administrations. The administration dose for a specific individual or patient should be decided based on various related factors such as the body weight, age, sex, health, diet, administration intervals, method of administration and severity of the illness, and may be appropriately increased or reduced by an expert. The administration doses stated above are not intended to limit the scope of the present invention in any manner. A physician or veterinarian have ordinary skill in related art may readily decide and prescribe an effective required dose for the pharmaceutical composition. For example, a physician or veterinarian may, beginning at levels less than that required for achieving the target therapeutic effect, gradually increase the dose of the compound of the present invention in a pharmaceutical composition until the intended effect is achieved.

[00237] The compounds and compositions of the present disclosure may be administered alone, in combination with a compound according to another example of the present disclosure, or in simultaneous, separate or sequential concomitant administration with at least one other therapeutic agent, for example with other pharmaceutical active ingredients such as eye disease therapeutic agents, antibiotics, anti-inflammatory agents and anti-microbials.

5.7. Definitions

[00238] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains.

[00239] It is understood that the definitions provided herein are not intended to be mutually exclusive. Accordingly, some chemical moieties may fall within the definition of more than one term.

[00240] The symbol " ⋯⋯ " refers to a covalent bond that is a single or a double bond.

[00241] The term "C_x-C_y" when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_1-C_6 alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from 1 to 6 carbons. In some embodiments, the term "(C_x-C_y)alkylene" refers to a substituted or unsubstituted alkylene chain with from x to y carbons in the alkylene chain. For example "(C_x-C_y)alkylene may be selected from methylene, ethylene, propylene, butylene, pentylene, and hexylene, any one of which is optionally substituted.

[00242] The term "alkyl" refers to an unbranched or branched saturated hydrocarbon chain. In some embodiments, alkyl as used herein has 1 to 20 carbon atoms ((C_1-C_{20})alkyl), 1 to 10 carbon atoms ((C_1-C_{10})alkyl), 1 to 8 carbon atoms ((C_1-C_8)alkyl), 1 to 6 carbon atoms ((C_1-C_6)alkyl), 1 to 5 carbon atoms ((C_1-C_5)alkyl) or 1 to 3 carbon atoms ((C_1-C_5)alkyl). Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 2-pentyl, isopentyl, neopentyl, n-hexyl, 2-hexyl, 3-hexyl, and 3-methyl pentyl. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons may be encompassed. For example, "butyl" can include n-butyl, sec-butyl, isobutyl and t-butyl, and "propyl" can include n-propyl and isopropyl. Unless stated otherwise specifically in the specification, an alkyl chain is optionally substituted by one or more substituents such as those substituents described herein.

[00243] The term "alkoxy" refers to an unbranched or branched alkyl group attached to an oxygen atom (alkyl-O-). In some embodiments, alkoxy as used herein has 1 to 20 carbon atoms ((C_1-C_{20})alkoxy), 1 to 10 carbon atoms ((C_1-C_{10})alkoxy), 1 to 8 carbon atoms ((C_1-C_8)alkoxy), 1 to 6 carbon atoms ((C_1-C_6)alkoxy), 1 to 5 carbon atoms ((C_1-C_5)alkoxy) or 1 to 3 carbon atoms ((C_1-C_3)alkoxy). Examples include, but are not limited to, methoxy, ethoxy, n-propoxy, and butoxy. When an alkoxy residue having a specific number of carbons is named, all geometric isomers having that number of carbons may be encompassed, such as isopropoxy, isobutoxy, and t-butoxy. Unless stated otherwise specifically in the specification, an alkoxy chain is optionally substituted by one or more substituents such as those substituents described herein.

[00244] The term "alkylene" refers to a straight divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation, and preferably having from 1 to 20 carbon atoms ((C_1-C_{20})alkylene), 1 to 10 carbon atoms ((C_1-

C_{10})alkylene), 1 to 6 carbon atoms ((C_1-C_6)alkylene), or 1 to 5 carbon atoms ((C_1-C_5)alkylene). Examples include, but are not limited to, methylene, ethylene, propylene, butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group are through the terminal carbons respectively. Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more substituents such as those substituents described herein. Examples include methylene (–CH_2–), ethylene (–CH_2CH_2–), propylene (–$CH_2CH_2CH_2$–), 2-methylpropylene (–CH_2–CH(CH_3) –CH_2–), hexylene (–$(CH_2)_6$–) and the like.

[00245] The term "alkenyl" refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond including straight-chain, branched-chain and cyclic alkenyl groups. In some embodiments, the alkenyl group has 2-10 carbon atoms ((C_2-C_{10}) alkenyl). In another embodiment, the alkenyl group has 2-4 carbon atoms in the chain ((C_2- C_4) alkenyl). Exemplary alkenyl groups include, but are not limited to, ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, cyclohexyl-butenyl and decenyl. An alkylalkenyl is an alkyl group as defined herein bonded to an alkenyl group as defined herein. The alkenyl group can be unsubstituted or substituted through available carbon atoms with one or more groups defined hereinabove for alkyl

[00246] The term "alkynyl" refers to straight or branched monovalent hydrocarbyl groups having from 2 to 6 carbon atoms and preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of acetylenic (C≡C–) unsaturation. Examples of such alkynyl groups include, but are not limited to, acetylenyl (C≡CH), and propargyl (CH_2C≡CH).

[00247] The term "aryl" refers to a monocyclic or polycyclic group having at least one hydrocarbon aromatic ring, wherein all of the ring atoms of the at least one hydrocarbon aromatic ring are carbon. Aryl may include groups with a single aromatic ring (e.g., phenyl) and multiple fused aromatic rings (e.g., naphthyl, anthryl). Aryl may further include groups with one or more aromatic hydrocarbon rings fused to one or more non-aromatic hydrocarbon rings (e.g., fluorenyl; 2,3-dihydro-1H-indene; 1,2,3,4-tetrahydronaphthalene). In certain embodiments, aryl includes groups with an aromatic hydrocarbon ring fused to a non-aromatic ring, wherein the non-aromatic ring comprises at least one ring heteroatom independently selected from the group consisting of N, O, and S. For example, in some embodiments, aryl includes groups with a phenyl ring fused to a non-aromatic ring, wherein the non-aromatic ring comprises at least one ring heteroatom independently selected from the group consisting of N, O, and S (e.g., chromane; thiochromane; 2,3-dihydrobenzofuran; indoline). In some embodiments, aryl as used herein has from 6 to 14 carbon atoms ((C_6-C_{14})aryl), or 6 to 10 carbon atoms ((C_6-C_{10})aryl). Where the aryl includes fused rings, the aryl may connect to one or more substituents or moieties of the formulae described herein through any atom of the fused ring for which valency permits.

[00248] The term "cycloalkyl" refers to a monocyclic or polycyclic saturated hydrocarbon. In some embodiments, cycloalkyl has 3 to 20 carbon atoms ((C_3-C_{20})cycloalkyl), 3 to 8 carbon atoms ((C_3-C_8)cycloalkyl), 3 to 6 carbon atoms ((C_3-C_6)cycloalkyl), or 3 to 5 carbon atoms ((C_3-C_5)cycloalkyl). In some embodiments, cycloalkyl has 3 to 8 carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. Examples of suitable cycloalkyl groups include, but are not limited to, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, octahydropentalenyl, octahydro-1*H*-indene, decahydronaphthalene, cubane, bicyclo[3.1.0]hexane, and bicyclo[1.1.1]pentane, and the like.

[00249] The term "carbocycle" refers to a saturated, unsaturated or aromatic ring system in which each atom of the ring system is carbon. Carbocycle includes 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. A bicyclic carbocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. A bicyclic carbocycle includes any combination of ring sizes such as 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, and naphthyl.

[00250] The term "haloalkyl" refers to a mono haloalkyl or a polyhaloalkyl group that can be further substituted or unsubstituted.

[00251] The term "heterocycle" refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. A bicyclic heterocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. In an exemplary embodiment, an aromatic ring, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, morpholine, piperidine or cyclohexene. A bicyclic heterocycle includes any combination of ring sizes such as 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems.

[00252] The term "heteroaryl" refers to an aromatic group of from 4 to 10 carbon atoms and 1 to 4 heteroatoms within the ring(s) (e.g., oxygen, nitrogen and/or sulfur). Such heteroaryl groups can have a single ring (i.e., pyridinyl or furyl) or multiple condensed rings (i.e., indolizinyl or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for

the N oxide (N→O), sulfinyl, or sulfonyl moieties. Examples of monocyclic heteroaryl include pyrazolyl, pyrrolyl, thiazolyl, oxazolyl, thiophenyl, furanyl, imidazolyl, isoxazolyl, triazolyl, thiadiazolyl, tetrazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, and similar groups, but are not limited to the aforementioned. Examples of bicyclic heteroaryl include indolyl, benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzothiadiazole, benzotriazolyl, quinolinyl, isoquinolinyl, purinyl, furopyridinyl, oxocromen, dioxoisoindolin, pyrazolopyridinyl, pyrazolo [1, 5-a] pyridinyl, and similar groups, but are not restricted to the aforementioned. Preferred heteroaryls include 5 or 6 membered heteroaryls such as pyridinyl, pyrrolyl, indolyl, thiophenyl, and furanyl.

[00253] The term "heteroalkyl" refers to an alkyl substituent in which one or more of the carbon atoms and any attached hydrogen atoms are independently replaced with the same or different heteroatomic group. For example, 1, 2, or 3 carbon atoms may be independently replaced with the same or different heteroatomic substituent.

[00254] The term "heterocycloalkyl" refers to substituted or unsubstituted monocyclic alkyl containing one or more hetero atoms (e.g., B, N, O, S, P(=O), Si or P). Examples include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, thiomorpholinyl, imidazolidinyl, tetrahydrofurfuryl, and similar groups, but are not restricted to the aforementioned.

[00255] The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., NH or NH_2, of a compound. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound. For example, stable compounds include, but is not limited to, compounds which do not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. The term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds.

[00256] It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to a "heteroaryl" group or moiety implicitly includes both substituted and unsubstituted variants, unless specified otherwise.

[00257] When referring to compound features, the phrase "optionally substituted" may be used interchangeably with the phrase "unsubstituted or substituted" and refers to when a non-hydrogen substituent may or may not be present on a given atom or group, and, thus, the description includes structures where a non-hydrogen substituent is present and structures where a non-hydrogen substituent is not present. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined herein. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[00258] In some embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazino (=N-NH_2), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^bN(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2). In another exemplary embodiment, substituents include alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, imino, oximo, hydrazine, $-R^bOR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and wherein each R^a, R^b, and R^c are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl; and wherein each R^a, R^b, and R^c, valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, imino, oximo, hydrazine, $-R^bOR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2).

[00259] The term "isomers" refers to two or more compounds comprising the same numbers and types of atoms, groups or components, but with different structural arrangement and connectivity of the atoms.

[00260] The term "tautomer" refers to one of two or more structural isomers which readily convert from one isomeric form to another and which exist in equilibrium.

[00261] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are non-superimposable mirror images of one another.

[00262] Individual enantiomers and diastereomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns, or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures also can be resolved into their respective enantiomers by well-known methods, such as chiral-phase gas chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations. See, for example, Carreira and Kvaerno, Classics in Stereoselective Synthesis, Wiley-VCH: Weinheim, 2009.

[00263] The symbol = denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration, where the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "E" and "Z" isomers.

[00264] Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituent on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compound wherein the substituents are disposed on both the same and opposite sides of the plane of the ring are designated "cis/trans."

[00265] Singular articles such as "a," "an" and "the" and similar referents in the context of describing the elements are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, including the upper and lower bounds of the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All

methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*i.e.*, "such as") provided herein, is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated.

[00266] In some embodiments, where the use of the term "about" is before a quantitative value, the present disclosure also includes the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term "about" refers to a ±10% variation from the nominal value unless otherwise indicated or inferred. Where a percentage is provided with respect to an amount of a component or material in a composition, the percentage should be understood to be a percentage based on weight, unless otherwise stated or understood from the context.

[00267] Where a molecular weight is provided and not an absolute value, for example, of a polymer, then the molecular weight should be understood to be an average molecule weight, unless otherwise stated or understood from the context.

[00268] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present disclosure remain operable. Moreover, two or more steps or actions can be conducted simultaneously.

[00269] A dash ("--") symbol that is not between two letters or symbols refers to a point of bonding or attachment for a substituent. For example, $-NH_2$ is attached through the nitrogen atom.

[00270] The term "pharmaceutically acceptable salt" refers to a salt which is acceptable for administration to a subject. It is understood that such salts, with counter ions, will have acceptable mammalian safety for a given dosage regime. Such salts can also be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically acceptable inorganic or organic acids, and may comprise organic and inorganic counter ions. The neutral forms of the compounds described herein may be converted to the corresponding salt forms by contacting the compound with a base or acid and isolating the resulting salts.

[00271] The terms "pharmaceutically acceptable excipient," "pharmaceutically acceptable diluent," "pharmaceutically acceptable carrier," and "pharmaceutically acceptable adjuvant" are used interchangeably and refer to an excipient, diluent, carrier, or adjuvant that is useful in preparing a pharmaceutical composition that are generally safe, non-toxic and neither biologically nor otherwise undesirable, and include an excipient, diluent, carrier, and adjuvant that are acceptable for veterinary use as well as human pharmaceutical use. The phrase "pharmaceutically acceptable excipient" includes both one and more than one such excipient, diluent, carrier, and/or adjuvant.

[00272] The term "pharmaceutical composition" is meant to encompass a composition suitable for administration to a subject, such as a mammal, especially a human. In general a "pharmaceutical composition" is sterile, and preferably free of contaminants that are capable of eliciting an undesirable response within the subject (*i.e.*, the compound(s) in the pharmaceutical composition is

pharmaceutical grade). Pharmaceutical compositions can be designed for administration to subjects or patients in need thereof *via* a number of different routes of administration including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, intratracheal, intramuscular, subcutaneous, and the like.

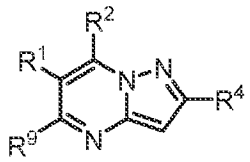
[00273] The terms "**individual**" and "**subject**" are used interchangeably and refer to a subject requiring treatment of a disease. More specifically, what is referred to is a human or non-human primate, mouse, dog, cat, horse, cow, rabbit, rat, or other mammal.

5.8. Exemplary Embodiments

[00274] As described herein, the text refers to various embodiments of the present compounds, compositions, and methods. The various embodiments described are meant to provide a variety of illustrative examples and should not be construed as descriptions of alternative species. Rather, it should be noted that the descriptions of various embodiments provided herein may be of overlapping scope. The embodiments discussed herein are merely illustrative and are not meant to limit the scope of the present technology.

[00275] Notwithstanding the appended claims, aspects of the present disclosure are illustrated by the following clauses.

[00276] Clause 1. A method of treating an inflammatory disease, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (Ia):



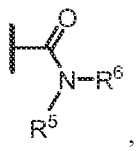
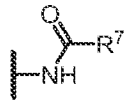
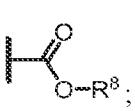
(Ia)

,

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

R^9 is selected from H and halogen.

[00277] Clause 2. The method of clause 1, wherein the subject has an inflammatory disease.

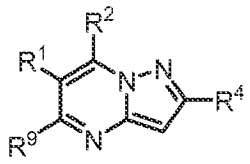
[00278] Clause 3. The method of clause 1 or 2, wherein the inflammatory disease is a chronic inflammatory disease.

[00279] Clause 4. The method of clause 1 or 2, wherein the inflammatory disease is an acute inflammatory disease.

[00280] Clause 5. The method of any one of clauses 1 to 4, wherein the inflammatory disease is selected from chronic obstructive pulmonary disease (COPD), asthma, inflammatory airway disease, psoriasis, psoriatic disorder, atopic dermatitis, inflammatory bowel disease (IBD), rheumatoid arthritis, ankylosing spondylitis, neuroinflammation, and conjunctivitis.

[00281] Clause 6. The method of any one of clauses 1 to 4, wherein the inflammatory disease is an inflammatory skin disease.

[00282] Clause 7. A method of treating a CFTR-related indication, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (Ia):

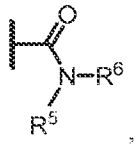
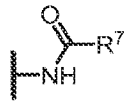


(Ia)

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

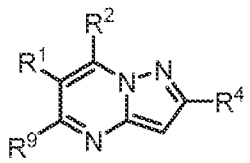
R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

R^9 is selected from H and halogen.

[00283] Clause 8. The method of clause 7, wherein the CFTR-related indication is selected from chronic obstructive pulmonary disease (COPD), asthma, bronchitis, bronchiectasis, celiac disease, constipation, cholestatic liver disease, chronic rhinosinusitis, and hepatic impairment.

[00284] Clause 9. A method of treating dry eye disease, the method comprising administering to an eye of a subject a therapeutically effective amount of a compound or a therapeutically effective amount of an ophthalmic composition comprising the compound, wherein the compound is of formula (Ia):

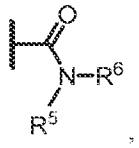
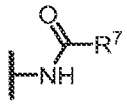
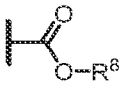


(Ia)

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

R^9 is selected from H and halogen.

[00285] Clause 10. The method of clause 9, further comprising identifying a subject suffering from dry eye disease.

[00286] Clause 11. The method of clause 9, further comprising identifying an underlying disease or condition associated with the dry eye disease.

[00287] Clause 12. The method of any one of clauses 9 to 11, wherein the dry eye disease is caused by one or more disease or condition of the group consisting of keratoconjunctivitis sicca, age-related dry eye, Stevens- Johnson syndrome, Sjogren's syndrome, ocular cicatrical pemphigoid, corneal injury, infection, Riley-Day syndrome, congenital alacrima, nutritional disorders or deficiencies, pharmacologic side effects, contact lens intolerance, eye stress resulting in glandular and tissue destruction, autoimmune disorders, immuno-deficient disorders, comatose patients who are unable to blink, or environmental exposure to smog, smoke, excessively dry air, airborne particulates, lacrimal deficiency, lacrimal gland duct obstruction, Meibomian oil deficiency, a disorder of eyelid aperture, and ocular surface disease (OSD).

[00288] Clause 13. The method of any one of clauses 9 to 11, wherein said dry eye disease is caused by keratoconjunctivitis sicca, age-related dry eye, Stevens- Johnson syndrome, Sjogren's syndrome, ocular cicatrical pemphigoid, corneal injury, Riley-Day syndrome, or congenital alacrima.

[00289] Clause 14. The method of any one of clauses 9 to 11, wherein said dry eye disease is caused by nutritional disorders or deficiencies, contact lens intolerance, autoimmune disorders, immuno-deficient disorders, comatose patients who are unable to blink, or environmental exposure to smog, smoke, excessively dry air, or airborne particulates.

[00290] Clause 15. The method of any one of clauses 9 to 14, whereby one or more dry eye symptoms are reduced or alleviated in the subject after administration.

[00291] Clause 16. The method of clause 15, wherein the one or more dry eye symptoms are selected from dryness, burning, ocular itching, photophobia, foreign body sensation, and grittiness.

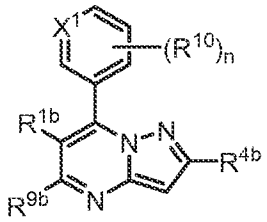
[00292] Clause 17. The method of any one of clauses 9 to 16, further comprising assessing restoration of the natural tear film in the eye after administration.

[00293] Clause 18. The method of any one of clauses 9 to 17, wherein the compound or the ophthalmic composition is topically administered to the eye.

[00294] Clause 19. The method of any one of clauses 1 to 18, wherein in formula (Ia), the R^2 is a substituted aryl with 1 to 3 substituents or a substituted heteroaryl with 1 to 3 substituents.

[00295] Clause 20. The method of clause 19, wherein the R^2 is an optionally substituted phenyl or an optionally substituted heteroaryl.

[00296] Clause 21. The method of clause 20, wherein the compound is of formula (Ib):

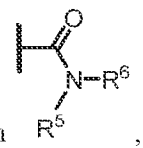
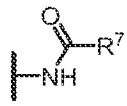
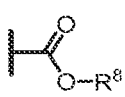


(Ib)

wherein:

X^1 is $CR^{10'}$ or N;

R^{1b} is selected from H, halogen, optionally substituted aryl, optionally substituted $(C_1\text{-}C_{10})$alkyl, and optionally substituted $(C_1\text{-}C_{10})$alkoxy;

R^{4b} is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted $(C_1\text{-}C_{10})$alkyl, optionally substituted $(C_1\text{-}C_{10})$alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl,

optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

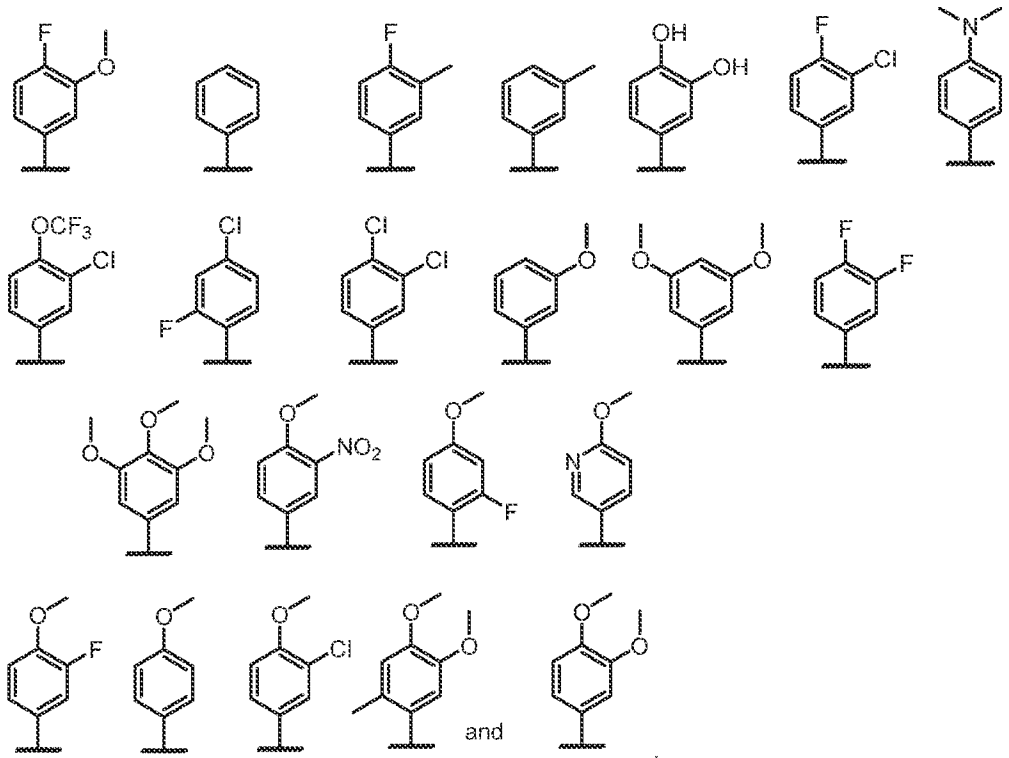
R^{9b} is selected from H and halogen;

each R^{10} and $R^{10'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

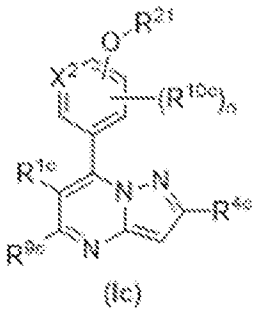
n is 0 to 4.

[00297] Clause 22. The method of clause 21, wherein each R^{10} and $R^{10'}$ is independently selected from H, OH, CH_3, CF_3, OCF_3, OCH_3, NO_2, F, and Cl, and dimethylamine.

[00298] Clause 23. The method of any one of clauses 20-22, wherein R^2 is selected from:



[00299] Clause 24. The method of clause 21 or 22, wherein the compound is of formula (Ic):



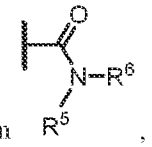
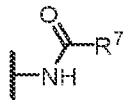
(Ic)

wherein:

X^2 is $CR^{10c'}$ or N;

R^{21} is selected from H, and optionally substituted (C_1-C_{10})alkyl; optionally substituted acyl; optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{1c} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4c} is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

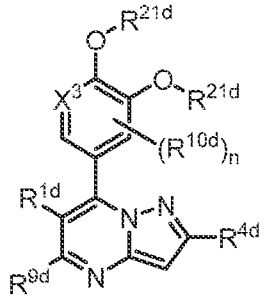
R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

R^{9c} is selected from H and halogen;

each R^{10c} and $R^{10c'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 3.

[00300] Clause 25. The method of clause 24, wherein the compound is of formula (Id):



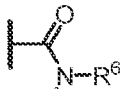
(Id)

wherein:

X^3 is $CR^{10d'}$ or N;

each R^{21d} is independently selected from H, and optionally substituted (C_1-C_{10})alkyl; optionally substituted acyl; optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{1d} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4d} is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

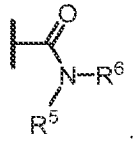
R^{9d} is selected from H and halogen;

each R^{10d} and $R^{10d'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 2.

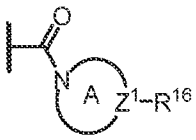
[00301] Clause 26. The method of clause 24 or 25, wherein R^{21}, or R^{21d} is methyl.

[00302] Clause 27. The method of any one of clauses 19 to 26, wherein any of R^4-R^{4d} is



[00303] Clause 28. The method of clause 27, wherein R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to provide an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle.

[00304] Clause 29. The method of clause 27 or 28, wherein R^4 is



wherein:

ring A is an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle;

Z^1 is CR^{14} or N, where R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle; and

R^{16} is selected from H, halogen, $-OR^{22a}$, $-C(O)R^{22b}$, $-CO_2R^{22c}$, and $-C(O)NR^{50}R^{60}$, $-NR^{50}R^{60}$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^{22a}, R^{22b}, and R^{22c} are independently selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

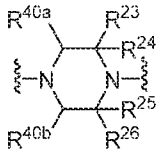
R^{50} and R^{60} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^{50} and R^{60} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted heterocycle, or an optionally substituted heteroaryl.

[00305] Clause 30. The method of clause 29, wherein when the A ring is piperidine, then R^{16} comprises at least one cyclic group selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle.

[00306] Clause 31. The method of clause 29, wherein the A ring is an optionally substituted piperazine, pyrrolidine, or azetidine.

[00307] Clause 32. The method of clause 31, wherein the A ring is:



wherein:

R^{23}-R^{26} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; or

one or both of R^{23}-R^{24} and R^{25}-R^{26} together with the carbon atom to which they are attached are cyclically linked to form an optionally substituted carbocycle or an optionally substituted heterocycle; and

R^{40a} and R^{40b} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle.

[00308] Clause 33. The method of clause 32, wherein:

R^{23} is selected from optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl; and

R^{24}-R^{26}, R^{40a} and R^{40b} are each H.

[00309] Clause 34. The method of clause 32, wherein:

two of R^{23}, R^{25}, and R^{40b} are independently selected from optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl;

the other one of R^{23}, R^{25} and R^{40b} is H; and

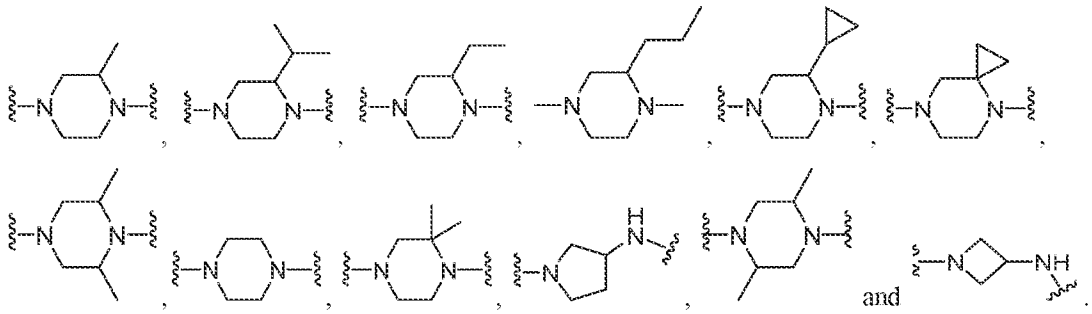
R^{24}, R^{26} and R^{40a} are each H.

[00310] Clause 35. The method of clause 32, wherein:

R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a carbocycle or R^{23} and R^{24} are each independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and

R^{25}-R^{26}, R^{40a} and R^{40b} are each H.

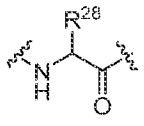
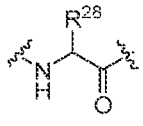
[00311] Clause 36. The method of any one of clauses 31-35, wherein the A ring is selected from:



[00312] Clause 37. The method of any one of clauses 29-36, wherein R^{16} is:

$-(R^{110})_nR^{210}$

wherein:

each R^{110} is independently selected from optionally substituted $(C_1$-$C_6)$alkyl,  , -$C(O)(R^{110a})n^1$, $-C(O)O(R^{110b})n^2$, $-S(O)(R^{110c})n^3$, $-SO_2(R^{110d})n^4$, and $-C(O)NR^{27}(R^{110e})n^5$; where R^{110a}-R^{110e} are each independently optionally substituted $(C_1$-$C_6)$alkyl,  ; R^{27}-R^{28} are each independently selected from H and optionally substituted $(C_1$-$C_6)$alkyl; and n-n^5 are each independently 0 to 3; and

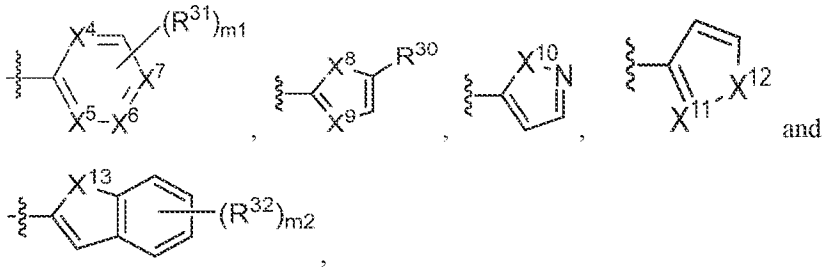
R^{210} is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle.

[00313] Clause 38. The method of clause 37, wherein:

R^{110} is selected from -C(O)-, -C(O)O-, -C(O)NH-, -S(O)-, and $-SO_2$-; and

R^{210} is selected from optionally substituted aryl and optionally substituted heteroaryl.

[00314] Clause 39. The method of clause 37 or 38, wherein R^{210} is selected from:



and

wherein:

X^4-X^7, X^9, and X^{11} are each independently selected from CH, CR^{31}, S, O, and N;

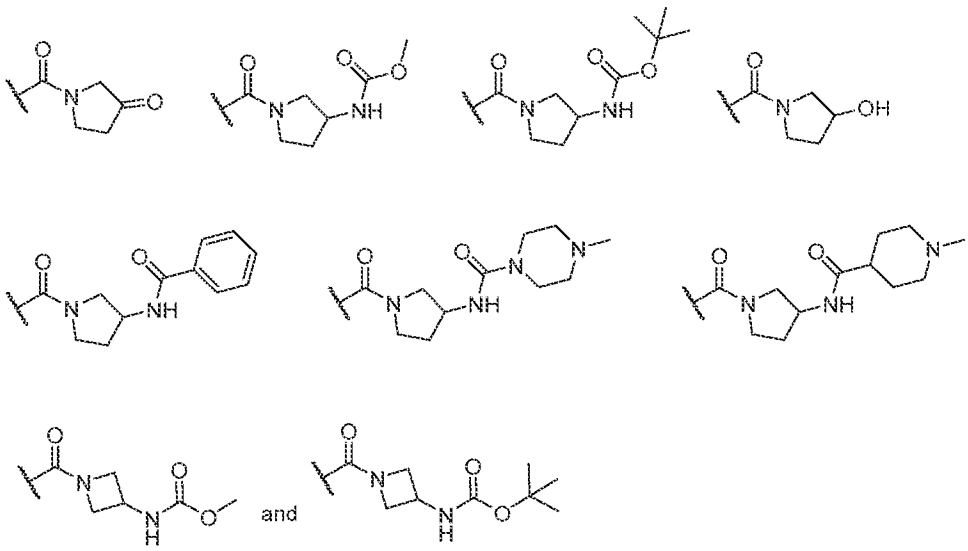
X^8, X^{10}, X^{12} and X^{13} are each independently selected from S, O, and NR^{29};

R^{29} is selected from H and optionally substituted $(C_1$-$C_6)$alkyl;

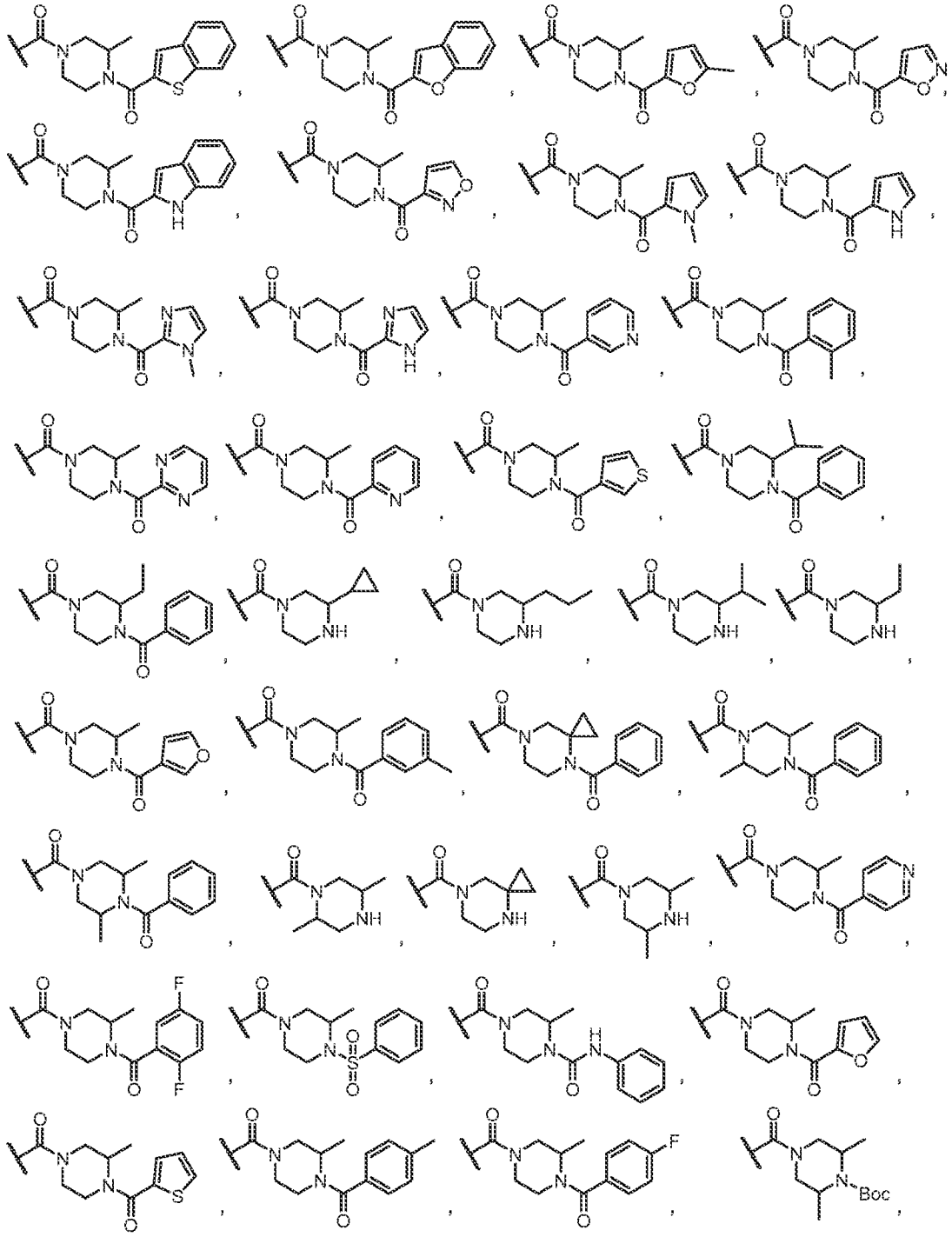
R^{30}-R^{32} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

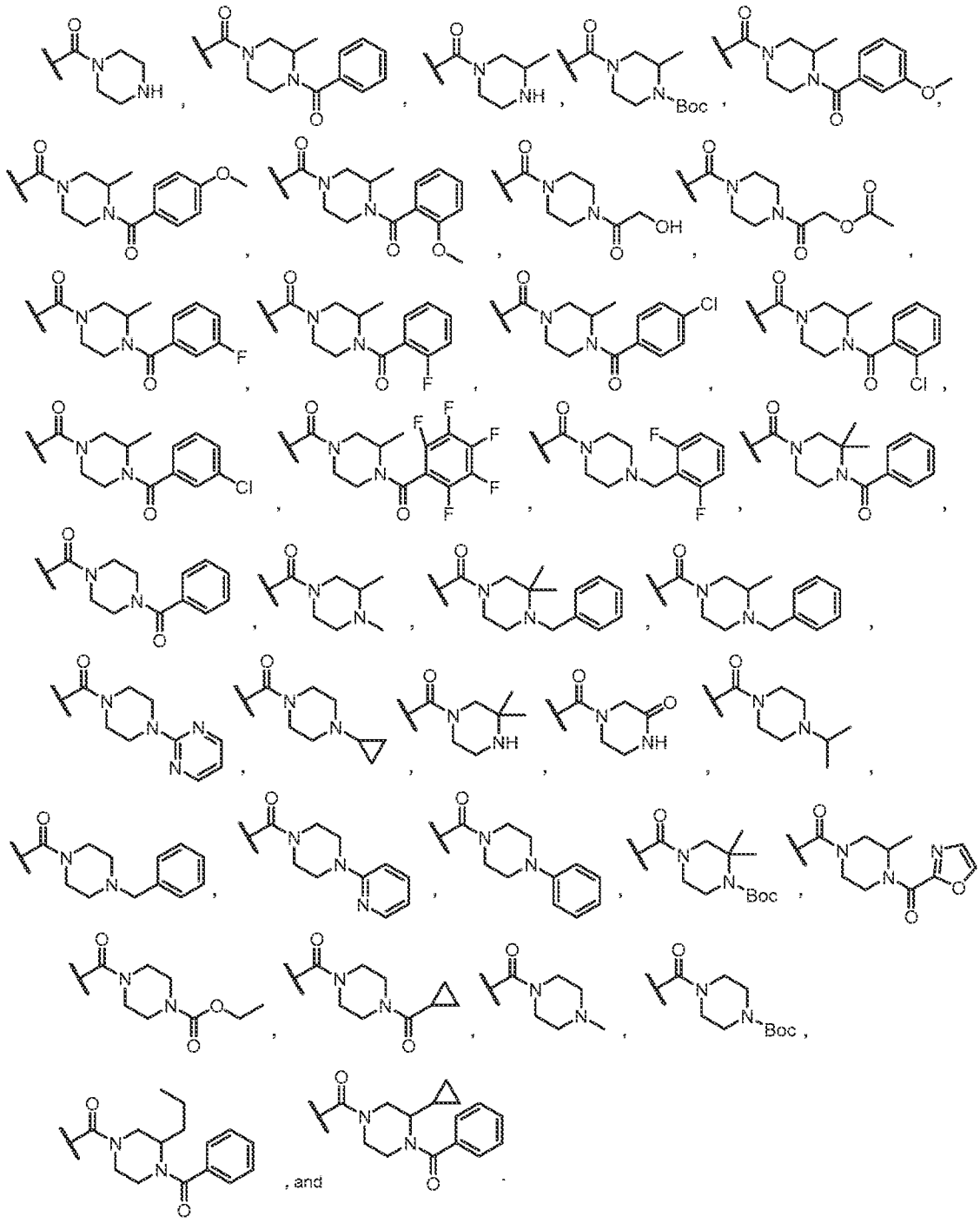
m^1-m^2 are each independently 0 to 5.

[00315] Clause 40. The method of clause 39, wherein any of R^4-R^{4d} is selected from:

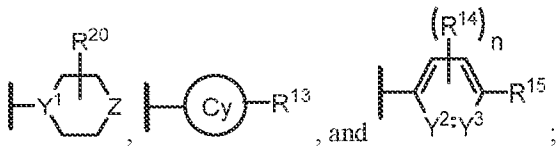


[00316] Clause 41. The method of clause 39, wherein any of R^4-R^{4d} is selected from:





[00317] Clause 42. The method of clause 27, wherein R^5 is H or Me, and R^6 is selected from:



wherein:

Y^1, Y^2, and Y^3 are independently selected from CR^{14} and N;

Z is selected from O, S, CHR^{11}, and NR^{12};

n is 0 to 4;

R^{11} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2a}, $C(O)R^{2b}$, CO_2R^{2c}, $C(O)NR^5R^6$, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, and optionally substituted heterocycle;

R^{12} is selected from H, NH_2, halogen, $C(O)R^{2d}$, CO_2R^{2e}, $C(O)NR^5R^6$, and optionally substituted (C_1-C_5)alkyl;

is selected from optionally substituted (C_1-C_6)alkyl-cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic (C_4-C_{10})carbocycle, and optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle;

R^{13} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2f}, $C(O)R^{2g}$, CO_2R^{2h}, $C(O)NR^5R^6$, NR^5R^6, $NHC(O)R^2$, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, and optionally substituted heterocycle;

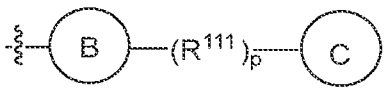
R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, CO_2R^2, $C(O)NR^5R^6$, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle;

R^{15} is selected from H, halogen, $NHC(O)R^{2i}$, OR^{2j}, $C(O)R^{2k}$, $OC(O)R^{2l}$ CO_2R^{2m}, $C(O)NR^5R^6$, NR^5R^6 optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, and optionally substituted heterocycle;

R^{20} is selected from H, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted carbocycle, and optionally substituted heterocycle; and

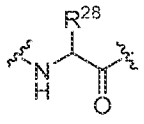
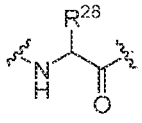
R^{2a}-R^{2m} are independently selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, heterocycle, heteroaryl, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy.

[00318] Clause 43. The method of clause 42, wherein R^6 is selected from:



wherein:

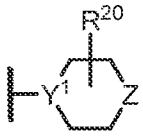
ring B and ring C are each independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle;

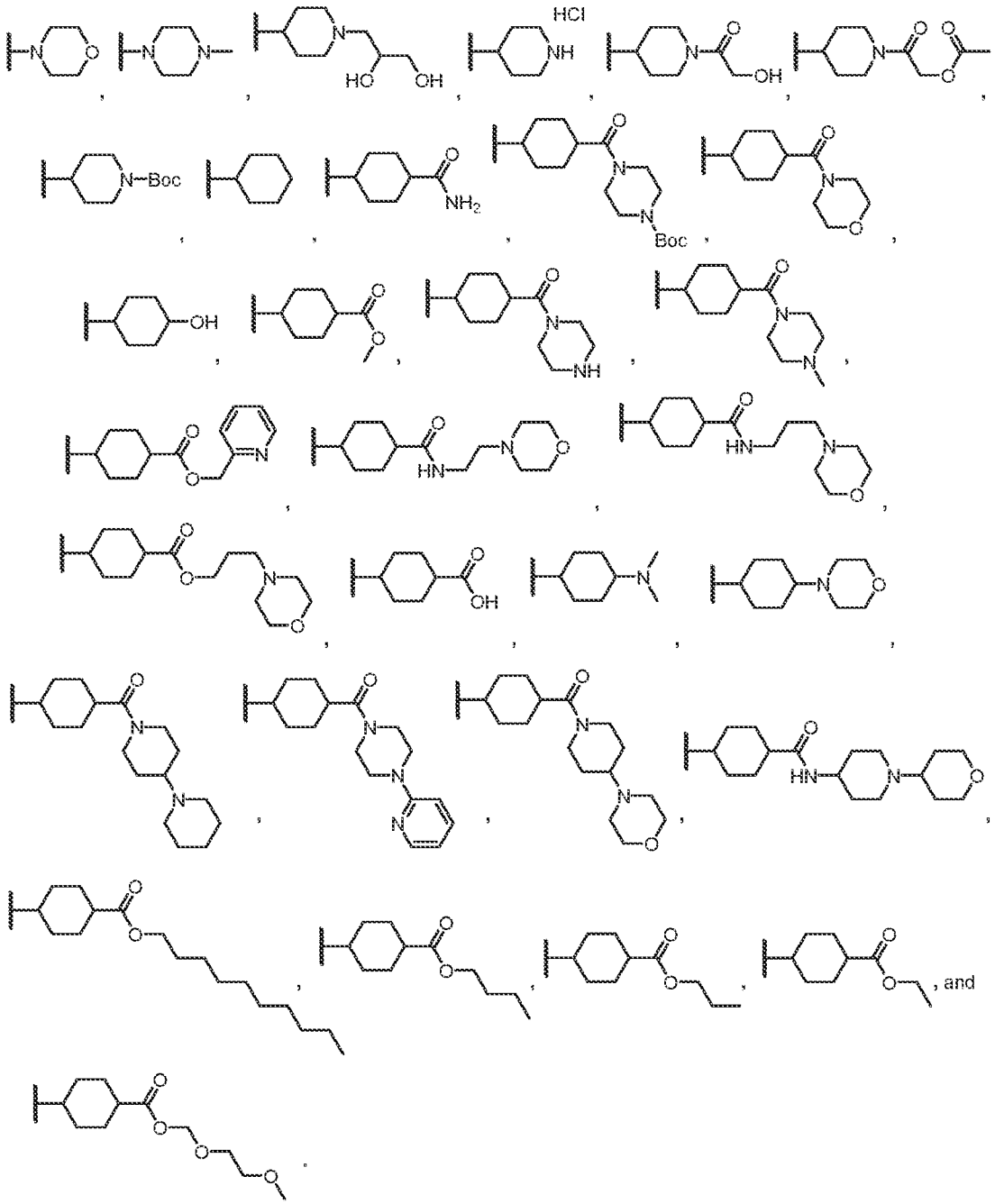
each R^{111} is independently selected from optionally substituted (C_1-C_6)alkyl,  , -C(O)(R^{111a})p^1, -C(O)O(R^{111b})p^2, -S(O)(R^{111c})p^3, -SO_2(R^{111d})p^4, and -C(O)NR^{27}(R^{111e})p^5; where R^{111a}-R^{111e} are each independently optionally substituted (C_1-C_6)alkyl,  ;

R^{27}-R^{28} are each independently selected from H and optionally substituted (C_1-C_6)alkyl; and

p-p^5 are each independently 0 to 3.

[00319] Clause 44. The method of clause 43, wherein one or both of the B ring and the C ring are optionally substituted piperazine.

[00320] Clause 45. The method of claim 43, wherein R^6 is  and is selected from:

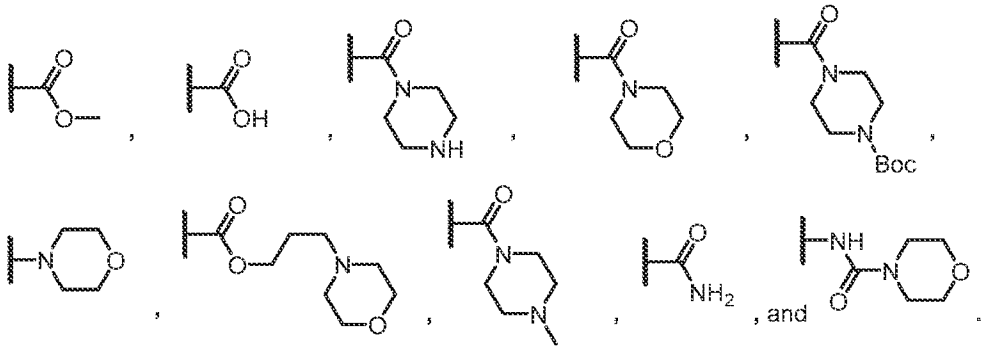


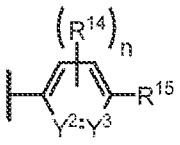
[00321] Clause 46. The method of clause 42, wherein R^6 is  and is selected from:  , and  .

[00322] Clause 47. The method of clause 46, wherein R^{13} is $-C(O)OR^{41a}$, $-NHC(O)R^{41b}$, $-C(O)NHR^{41c}$, $C(O)R^{41d}$, $C(O)NH_2$, heterocycle (e.g., morpholine, piperidine, morpholine-3-one), wherein R^{41a}-R^{41d} are independently selected from H, optionally substituted (C_1-C_6)alkyl, optionally

substituted heterocycle (e.g., morpholine, piperidine, morpholine-3-one), and optionally substituted (C_1-C_6)alkyl-heterocycle.

[00323] Clause 48. The method of clause 46 or 47, wherein R^{13} is selected from:



[00324] Clause 49. The method of clause 42, wherein R^6 is  .

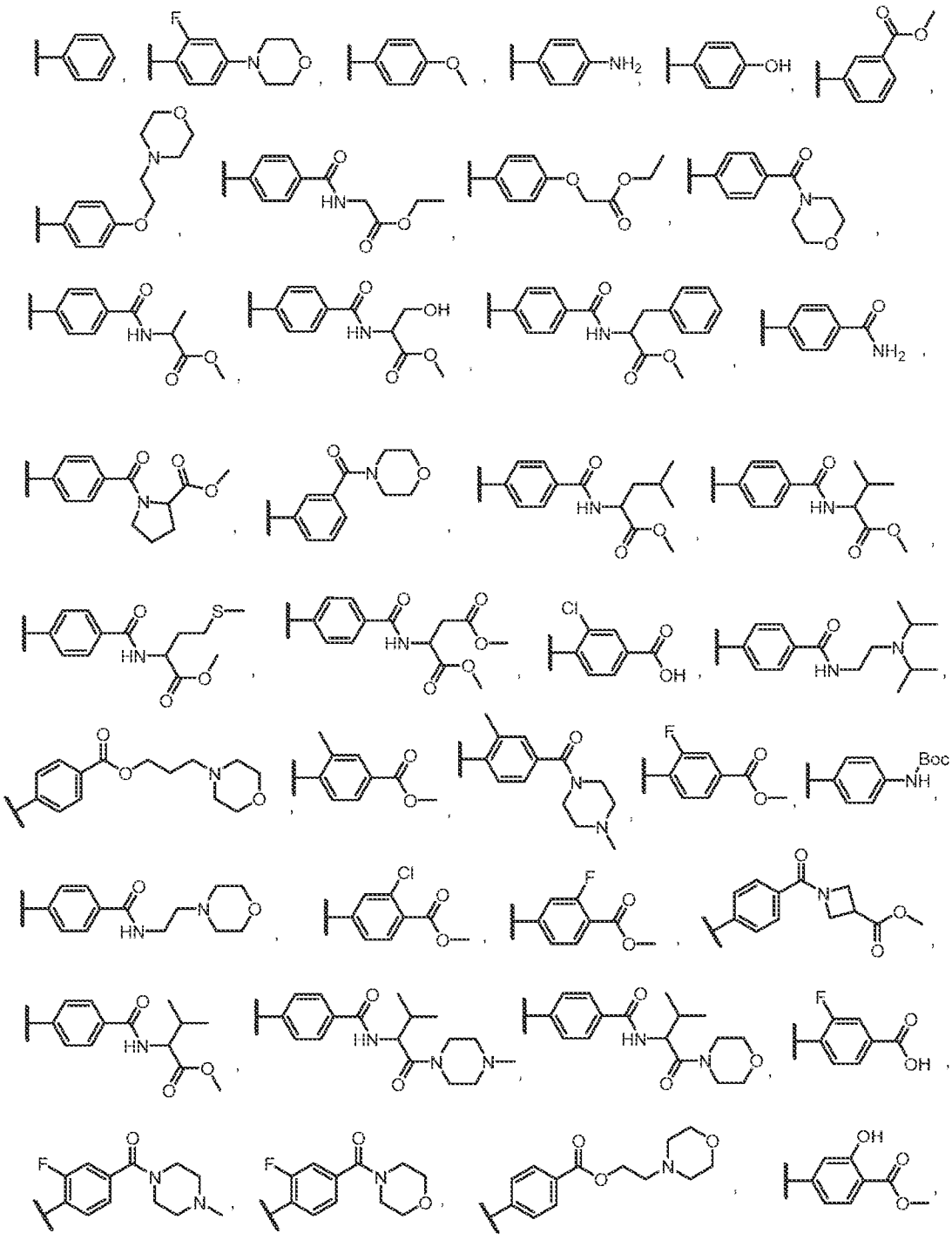
[00325] Clause 50. The method of clause 49, wherein Y^2 and Y^3 are each CR^{14}.

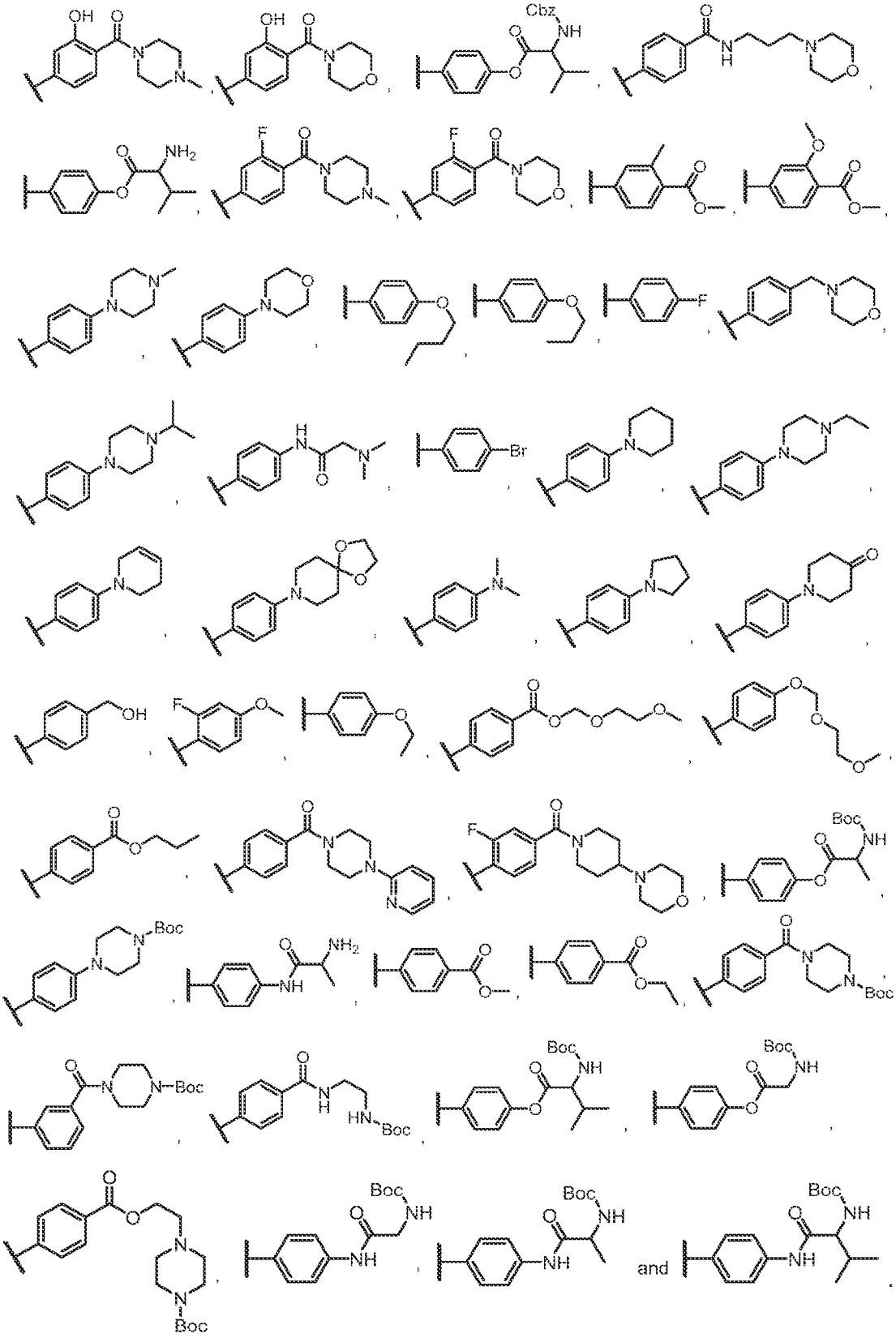
[00326] Clause 51. The method of clause 49 or 50, wherein:

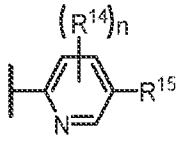
each R^{14} is independently selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, -$C(O)R^{42f}$, -$OC(O)R^{42g}$, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy; and

R^{15} is selected from H, halogen, -$OC(O)R^{42a}$, -$C(O)R^{42b}$, -$C(O)NHR^{42c}$, R^{42d} or -OR^{42e}, wherein R^{42a} to R^{42g} are independently selected from -OH, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted heterocycle, optionally substituted -O-(C_1-C_6)alkyl-heterocycle, and amino acid.

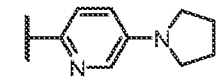
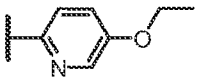
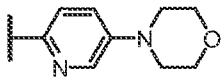
[00327] Clause 52. The method of any one of clauses 49 to 51, wherein R^6 is selected from:

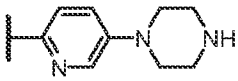
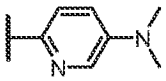
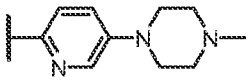


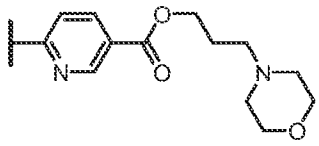
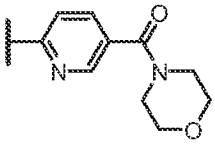
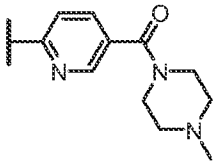
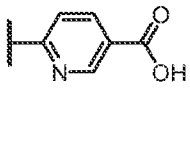


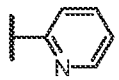
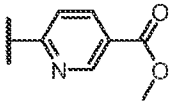
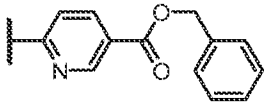
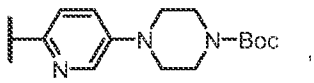
[00328] Clause 53. The method of clause 42, wherein R^6 is  and n is 0 to 3.

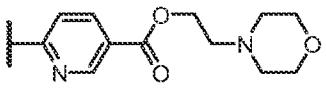
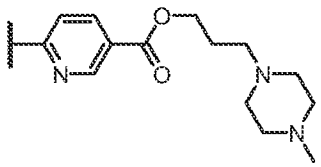
[00329] Clause 54. The method of clause 53, wherein R^6 is selected from:

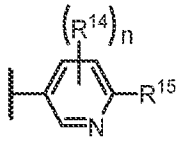
 ,  ,  ,  ,

 ,  ,  ,  ,

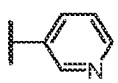
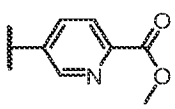
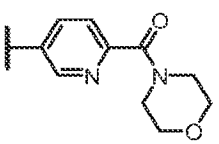
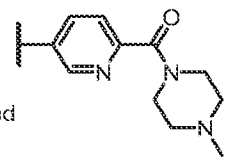
 ,  ,  ,  ,

 ,  ,  ,  ,

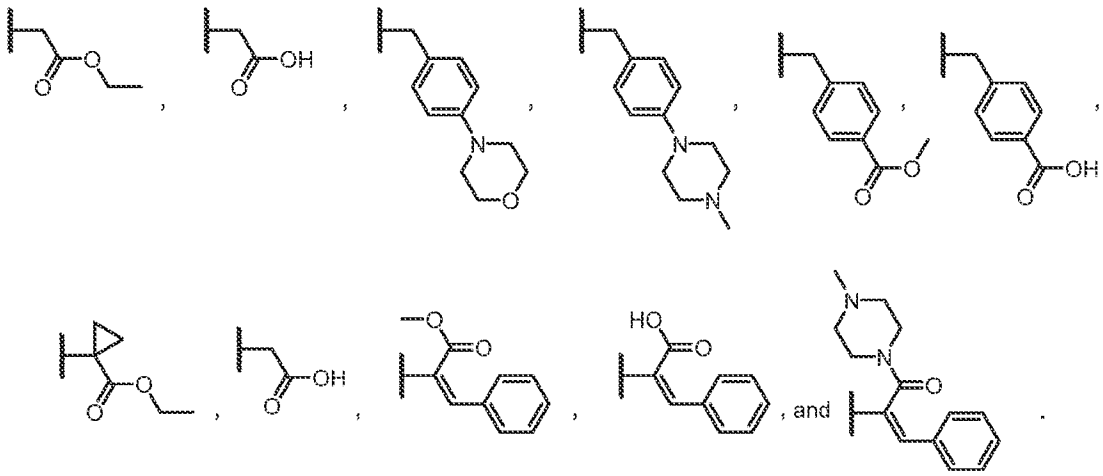
 and  .

[00330] Clause 55. The method of clause 42, wherein R^6 is  and n is 0 to 3.

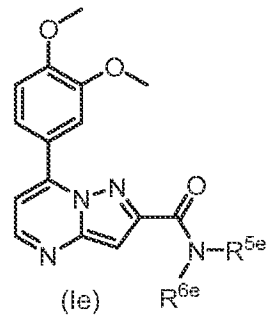
[00331] Clause 56. The method of clause 55, wherein R^6 is selected from:

 ,  ,  , and  .

[00332] Clause 57. The method of any one of clauses 19 to 28, wherein R^5 is H or Me, and R^6 is selected from:



[00333] Clause 58. The method of any one of clauses 19-57, wherein the compound is of formula (Ie):



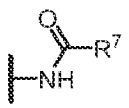
(Ie)

wherein:

R^{5e} and R^{6e} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

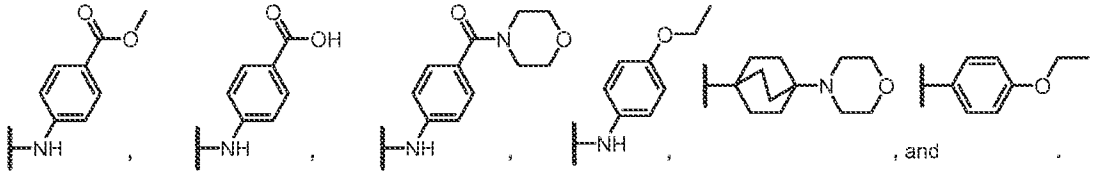
or R^{5e} and R^{6e} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle.

[00334] Clause 59. The method of any one of clauses 19 to 28, wherein any of R^4-R^{4d} is



[00335] Clause 60. The method of clause 59, wherein R^7 is selected from optionally substituted N-anilino, optionally substituted phenyl and optionally substituted bicyclic carbocycle.

[00336] Clause 61. The method of clause 59, wherein R^7 is selected from:



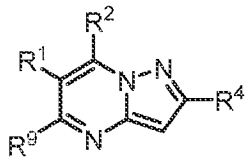
[00337] Clause 62. The method of any one of clauses 19 to 61, wherein the compound is of Table 1.

[00338] Clause 63. A compound, wherein the compound is selected from compounds 350 to 395 of Table 1, or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof.

[00339] Clause 64. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of clause 63, or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof; and a pharmaceutically acceptable excipient.

[00340]

[00341] Clause 65. A compound of formula (Ia):



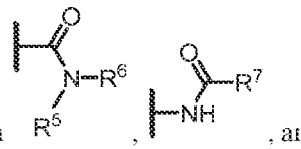
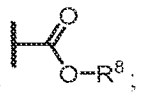
(Ia)

,

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

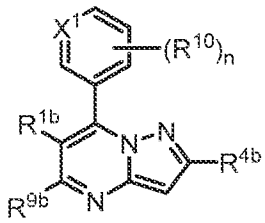
R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

R^9 is selected from H and halogen.

[00342] Clause 66. The compound of clause 65, wherein the R^2 is a substituted aryl with 1 to 3 substituents or a substituted heteroaryl with 1 to 3 substituents.

[00343] Clause 67. The compound of clause 65, wherein the R^2 is an optionally substituted phenyl or an optionally substituted heteroaryl.

[00344] Clause 68. The compound of clause 67, wherein the compound is of formula (Ib):



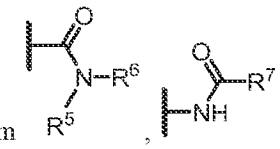
(Ib)

,

wherein:

X^1 is $CR^{10'}$ or N;

R^{1b} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4b} is selected from  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

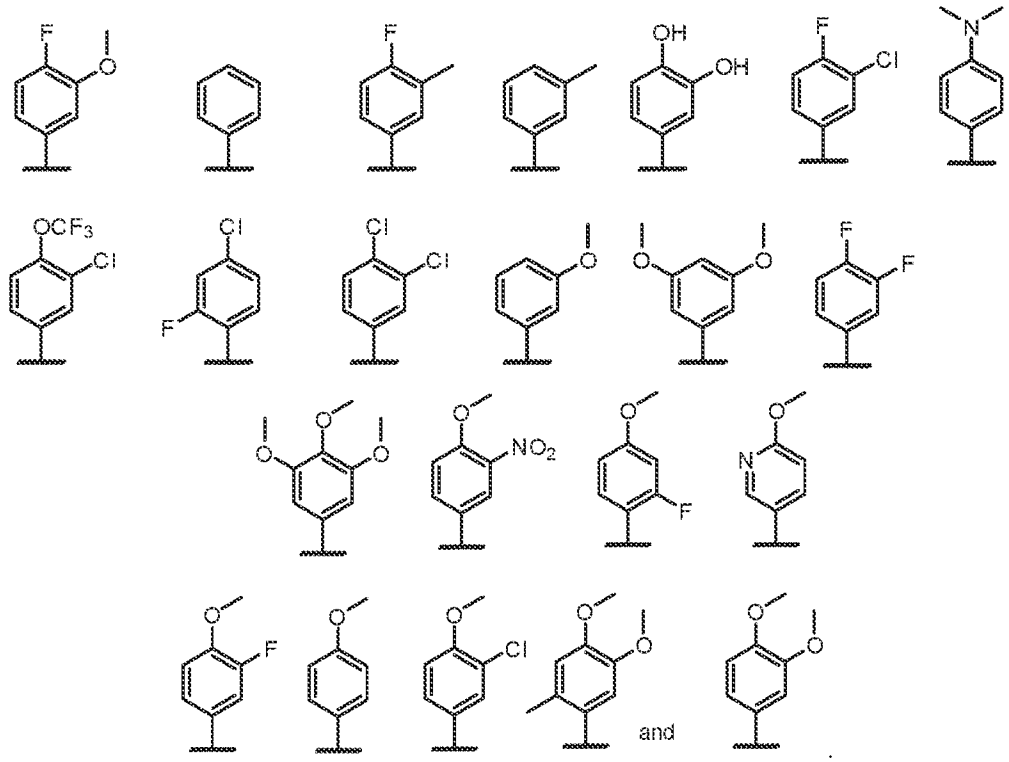
R^{9b} is selected from H and halogen;

each R^{10} and $R^{10'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

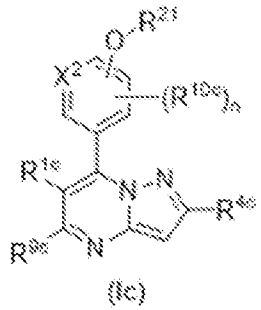
n is 0 to 4.

[00345] Clause 69. The compound of clause 68, wherein each R^{10} and $R^{10'}$ is independently selected from H, OH, CH_3, CF_3, OCF_3, OCH_3, NO_2, F, and Cl, and dimethylamine.

[00346] Clause 70. The compound of any one of clauses 67-69, wherein R^2 is selected from:



[00347] Clause 71. The compound of clause 69 or 70, wherein the compound is of formula (Ic):



(Ic)

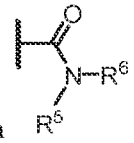
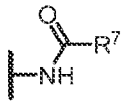
wherein:

X^2 is $CR^{10c'}$ or N;

R^{21} is selected from H, and optionally substituted (C_1-C_{10})alkyl; optionally substituted acyl;

optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{1c} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4c} is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

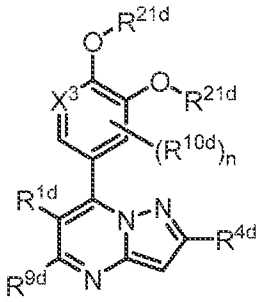
R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

R^{9c} is selected from H and halogen;

each R^{10c} and $R^{10c'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 3.

[00348] Clause 72. The compound of clause 71, wherein the compound is of formula (Id):



(Id) ,

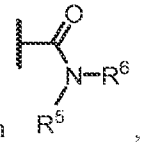
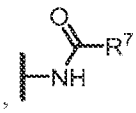
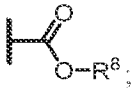
wherein:

X^3 is $CR^{10d'}$ or N;

each R^{21d} is independently selected from H, and optionally substituted (C_1-C_{10})alkyl; optionally substituted acyl; optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl,

optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{1d} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4d} is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

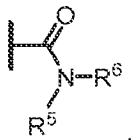
R^{9d} is selected from H and halogen;

each R^{10d} and $CR^{10d'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 2.

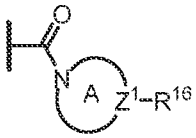
[00349] Clause 73. The compound of clause 71 or 72, wherein R^{21}, or R^{21d} is methyl.

[00350] Clause 74. The compound of any one of clauses 65 to 73, wherein any of R^4-R^{4d} is

 .

[00351] Clause 75. The compound of clause 74, wherein R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to provide an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle.

[00352] Clause 76. The compound of clause 74 or 75, wherein R^4 is



wherein:

ring A is an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle;

Z^1 is CR^{14} or N, where R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle; and

R^{16} is selected from H, halogen, $-OR^{22a}$, $-C(O)R^{22b}$, $-CO_2R^{22c}$, and $-C(O)NR^{50}R^{60}$, $-NR^{50}R^{60}$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^{22a}, R^{22b}, and R^{22c} are independently selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

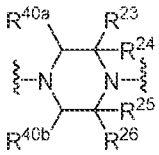
R^{50} and R^{60} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^{50} and R^{60} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted heterocycle, or an optionally substituted heteroaryl.

[00353] Clause 77. The compound of clause 76, wherein when the A ring is piperidine, then R^{16} comprises at least one cyclic group selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle.

[00354] Clause 78. The compound of clause 76, wherein the A ring is an optionally substituted piperazine, pyrrolidine, or azetidine.

[00355] Clause 79. The compound of clause 78, wherein the A ring is:



wherein:

R^{23}-R^{26} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; or

one or both of R^{23}-R^{24} and R^{25}-R^{26} together with the carbon atom to which they are attached are cyclically linked to form an optionally substituted carbocycle or an optionally substituted heterocycle; and

R^{40a} and R^{40b} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle.

[00356] Clause 80. The compound of clause 79, wherein:

R^{23} is selected from optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl; and

R^{24}-R^{26}, R^{40a} and R^{40b} are each H.

[00357] Clause 81. The compound of clause 79, wherein:

two of R^{23}, R^{25}, and R^{40b} are independently selected from optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl;

the other one of R^{23}, R^{25} and R^{40b} is H; and

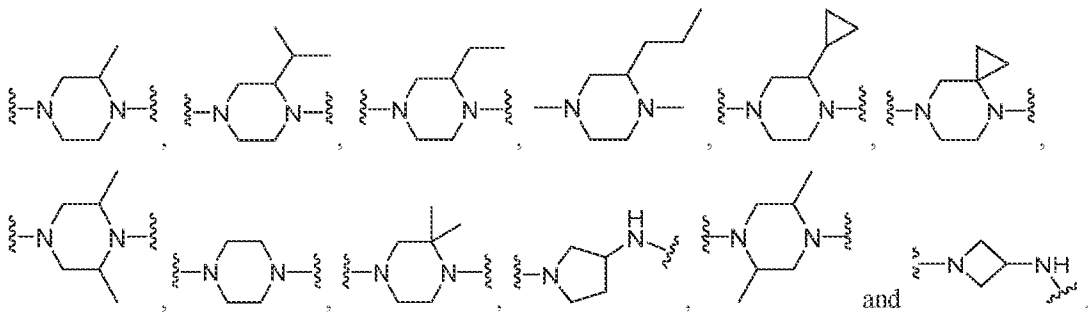
R^{24}, R^{26} and R^{40a} are each H.

[00358] Clause 82. The compound of clause 79, wherein:

R^{23} and R^{24} together with the carbon atom to which they are attached are cyclically linked to form a carbocycle or R^{23} and R^{24} are each independently selected from optionally substituted (C_1-C_6)alkyl and optionally substituted cycloalkyl; and

R^{25}-R^{26}, R^{40a} and R^{40b} are each H.

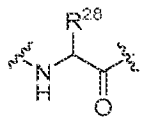
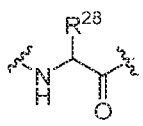
[00359] Clause 83. The compound of any one of clauses 78-82, wherein the A ring is selected from:


and

[00360] Clause 84. The compound of any one of clauses 76-83, wherein R^{16} is:

$$-(R^{110})_nR^{210}$$

wherein:

each R^{110} is independently selected from optionally substituted (C_1-C_6)alkyl,  , -C(O)(R^{110a})n^1, -C(O)O(R^{110b})n^2, -S(O)(R^{110c})n^3, -SO_2(R^{110d})n^4, and -C(O)NR^{27}(R^{110e})n^5; where R^{110a}-R^{110e} are each independently optionally substituted (C_1-C_6)alkyl,  ; R^{27}-R^{28} are each

independently selected from H and optionally substituted (C_1-C_6)alkyl; and n-n^5 are each independently 0 to 3; and

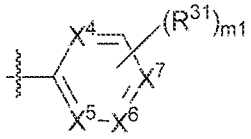
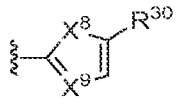
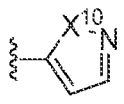
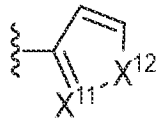
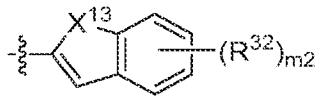
R^{210} is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle.

[00361] Clause 85. The compound of clause 84, wherein:

R^{110} is selected from -C(O)-, -C(O)O-, -C(O)NH-, -S(O)-, and -SO_2-; and

R^{210} is selected from optionally substituted aryl and optionally substituted heteroaryl.

[00362] Clause 86. The compound of clause 84 or 85, wherein R^{210} is selected from:





and


wherein:

X^4-X^7, X^9, and X^{11} are each independently selected from CH, CR^{31}, S, O, and N;

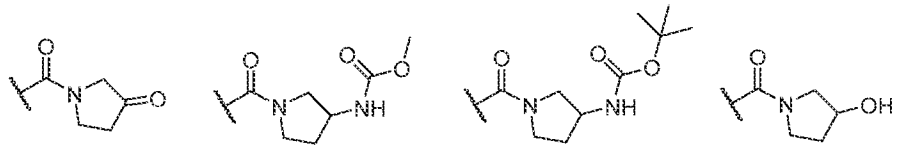
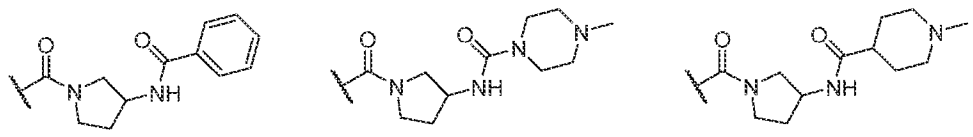
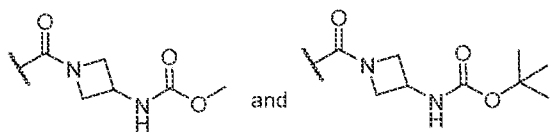
X^8, X^{10}, X^{12} and X^{13} are each independently selected from S, O, and NR^{29};

R^{29} is selected from H and optionally substituted (C_1-C_6)alkyl;

R^{30}-R^{32} are each independently selected from H, halogen, OH, NO_2, OCF_3, CF_3, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

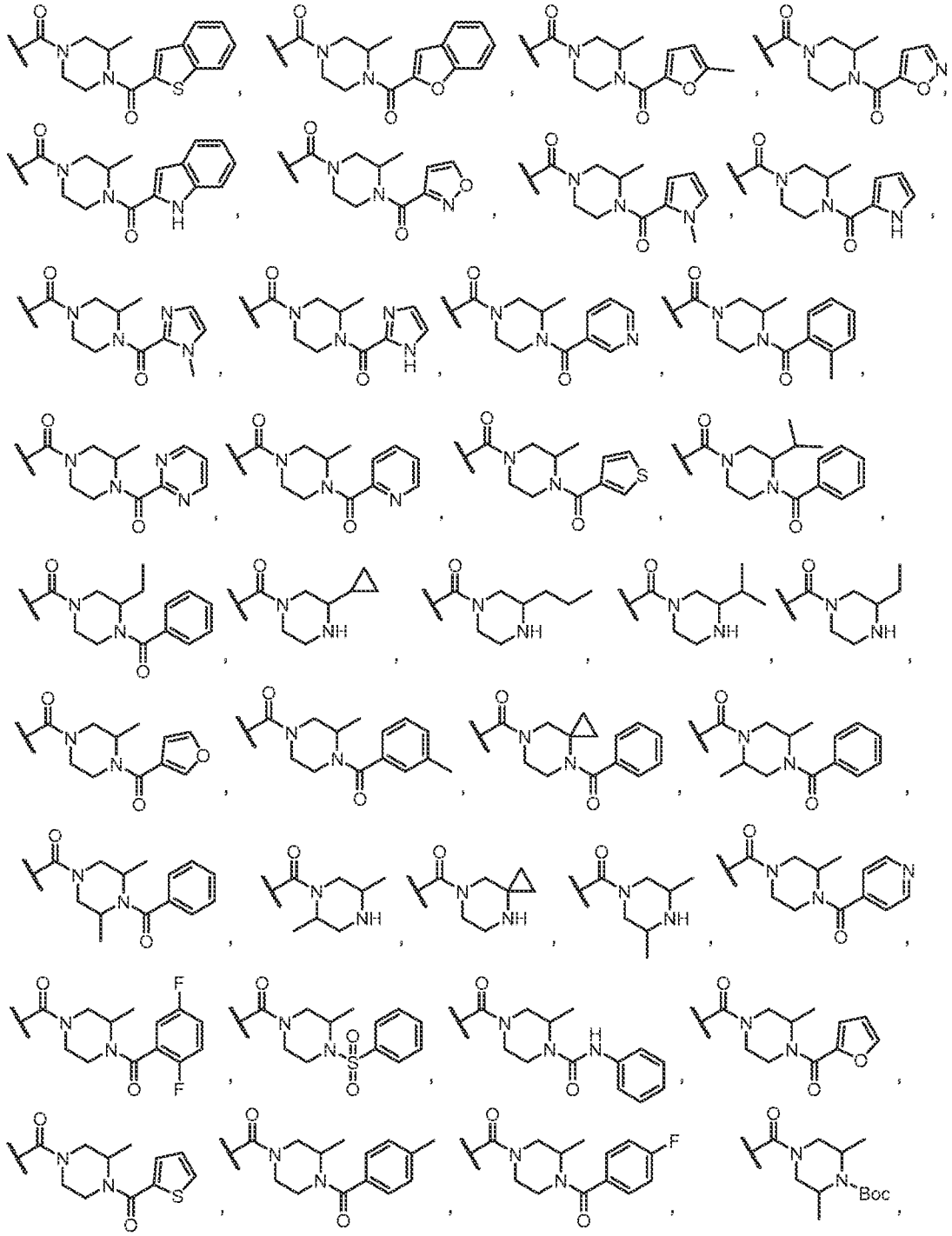
m^1-m^2 are each independently 0 to 5.

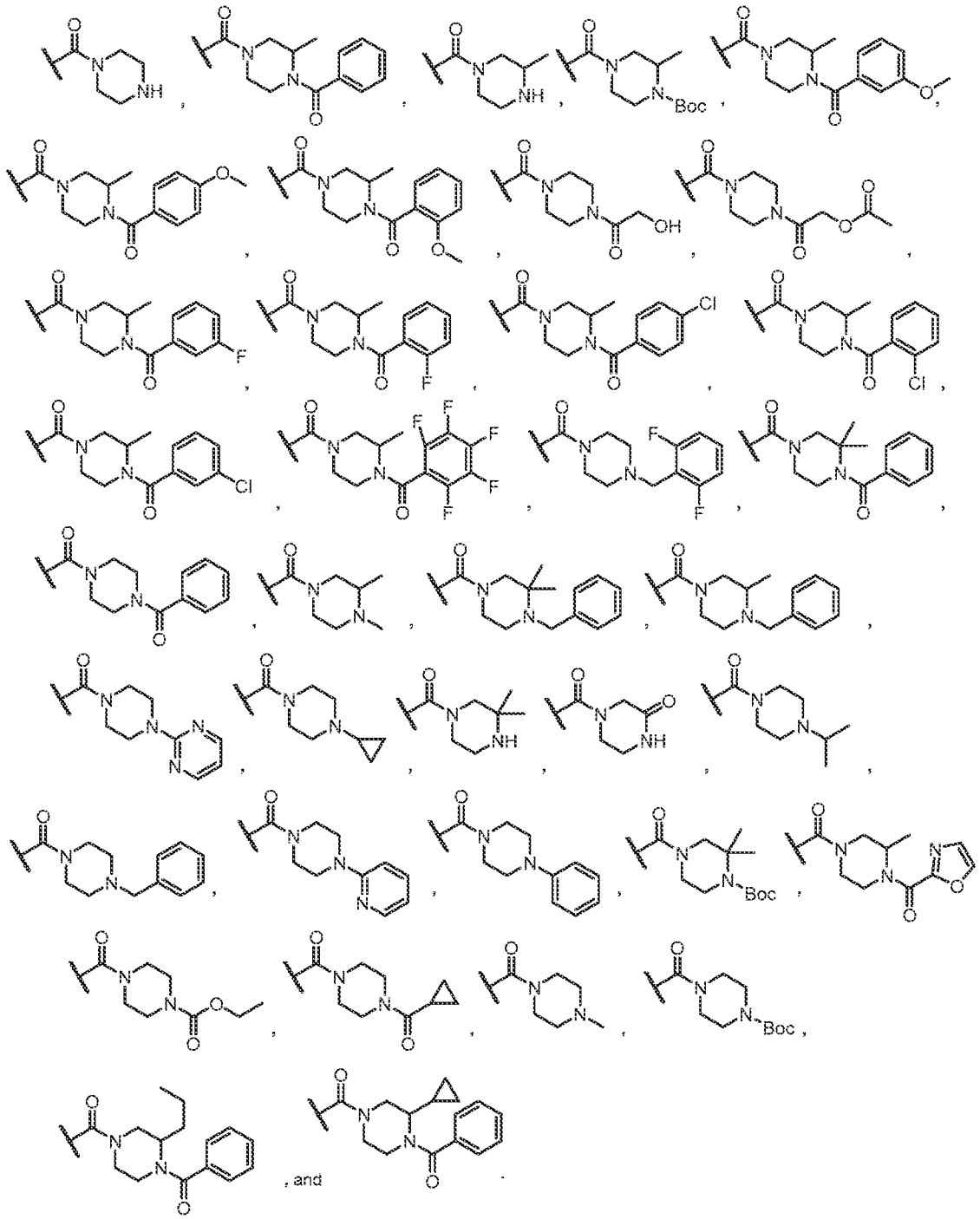
[00363] Clause 87. The compound of clause 76, wherein any of R^4-R^{4d} is selected from:




and

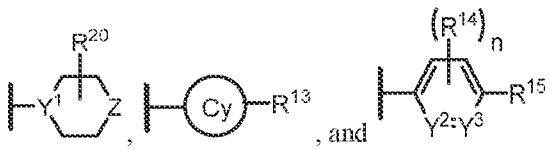
.

[00364] Clause 88. The compound of clause 76, wherein any of R^4-R^{4d} is selected from:





[00365] Clause 89. The compound of clause 74, wherein R^5 is H or Me, and R^6 is selected from:



wherein:

Y^1, Y^2, and Y^3 are independently selected from CR^{14} and N;

Z is selected from O, S, CHR^{11}, and NR^{12};

n is 0 to 4;

R^{11} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2a}, $C(O)R^{2b}$, CO_2R^{2c}, $C(O)NR^5R^6$, optionally substituted amino, optionally substituted $(C_1$-$C_5)$alkyl, and optionally substituted $(C_1$-$C_5)$alkoxy, and optionally substituted heterocycle;

R^{12} is selected from H, NH_2, halogen, $C(O)R^{2d}$, CO_2R^{2e}, $C(O)NR^5R^6$, and optionally substituted $(C_1$-$C_5)$alkyl;

is selected from optionally substituted $(C_1$-$C_6)$alkyl-cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic $(C_4$-$C_{10})$carbocycle, and optionally substituted monocyclic or bicyclic $(C_4$-$C_{10})$heterocycle;

R^{13} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2f}, $C(O)R^{2g}$, CO_2R^{2h}, $C(O)NR^5R^6$, NR^5R^6, $NHC(O)R^2$, optionally substituted $(C_1$-$C_5)$alkyl, and optionally substituted $(C_1$-$C_5)$alkoxy, and optionally substituted heterocycle;

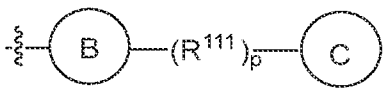
R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, CO_2R^2, $C(O)NR^5R^6$, optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted $(C_1$-$C_5)$alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle;

R^{15} is selected from H, halogen, $NHC(O)R^{2i}$, OR^{2j}, $C(O)R^{2k}$, $OC(O)R^{2l}$ CO_2R^{2m}, $C(O)NR^5R^6$, NR^5R^6 optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted $(C_1$-$C_5)$alkoxy, optionally substituted cycloalkyl, and optionally substituted heterocycle;

R^{20} is selected from H, halogen, optionally substituted $(C_1$-$C_5)$alkyl, optionally substituted $(C_1$-$C_5)$alkoxy, optionally substituted carbocycle, and optionally substituted heterocycle; and

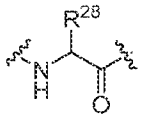
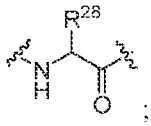
R^{2a}-R^{2m} are independently selected from H, optionally substituted $(C_1$-$C_{10})$ alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, heterocycle, heteroaryl, optionally substituted amino, optionally substituted $(C_1$-$C_5)$alkyl, and optionally substituted $(C_1$-$C_5)$alkoxy.

[00366] Clause 90. The compound of clause 89, wherein R^6 is selected from:



wherein:

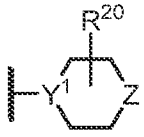
ring B and ring C are each independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle and optionally substituted heterocycle;

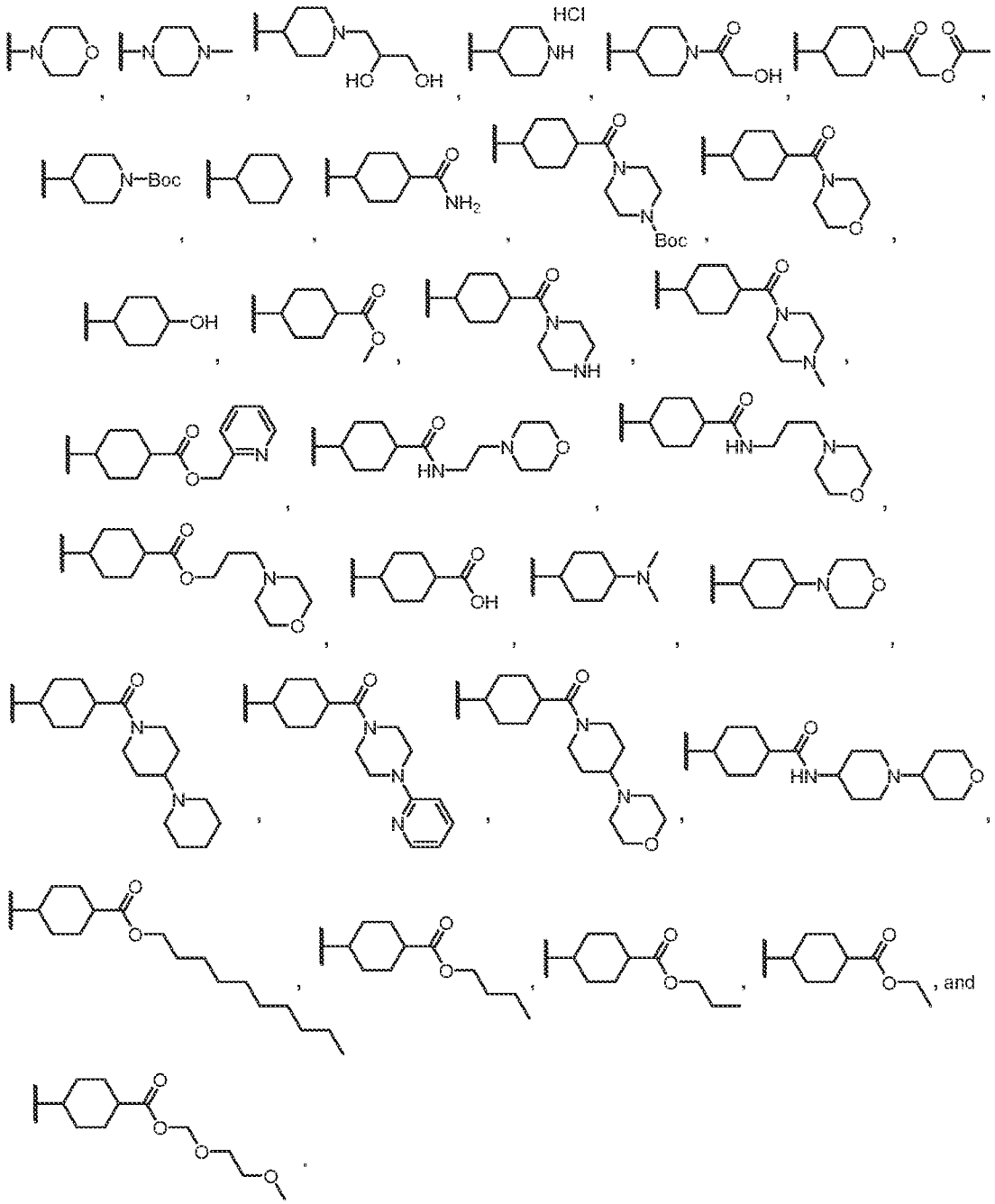
each R^{111} is independently selected from optionally substituted (C_1-C_6)alkyl,  , -C(O)(R^{111a})p^1, -C(O)O(R^{111b})p^2, -S(O)(R^{111c})p^3, -SO_2(R^{111d})p^4, and -C(O)NR^{27}(R^{111e})p^5; where R^{111a}-R^{111e} are each independently optionally substituted (C_1-C_6)alkyl,  ;

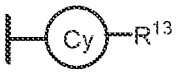
R^{27}-R^{28} are each independently selected from H and optionally substituted (C_1-C_6)alkyl; and

p-p^5 are each independently 0 to 3.

[00367] Clause 91. The compound of clause 90, wherein one or both of the B ring and the C ring are optionally substituted piperazine.

[00368] Clause 92. The compound of clause 90, wherein R^6 is  and is selected from:

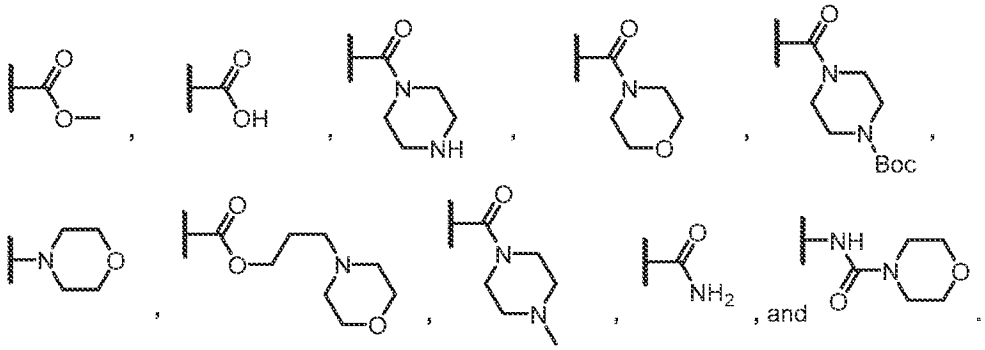


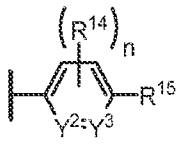
[00369] Clause 93. The compound of clause 89, wherein R^6 is  and is selected from:  , and  .

[00370] Clause 94. The compound of clause 93, wherein R^{13} is $-C(O)OR^{41a}$, $-NHC(O)R^{41b}$, $-C(O)NHR^{41c}$, $C(O)R^{41d}$, $C(O)NH_2$, heterocycle (e.g., morpholine), wherein R^{41a}-R^{41d} are

independently selected from H, optionally substituted (C_1-C_6)alkyl, optionally substituted heterocycle (e.g., morpholine, piperidine, morpholine-3-one), and optionally substituted (C_1-C_6)alkyl-heterocycle.

[00371] Clause 95. The compound of clause 93 or 94, wherein R^{13} is selected from:



[00372] Clause 96. The compound of clause 89, wherein R^6 is  .

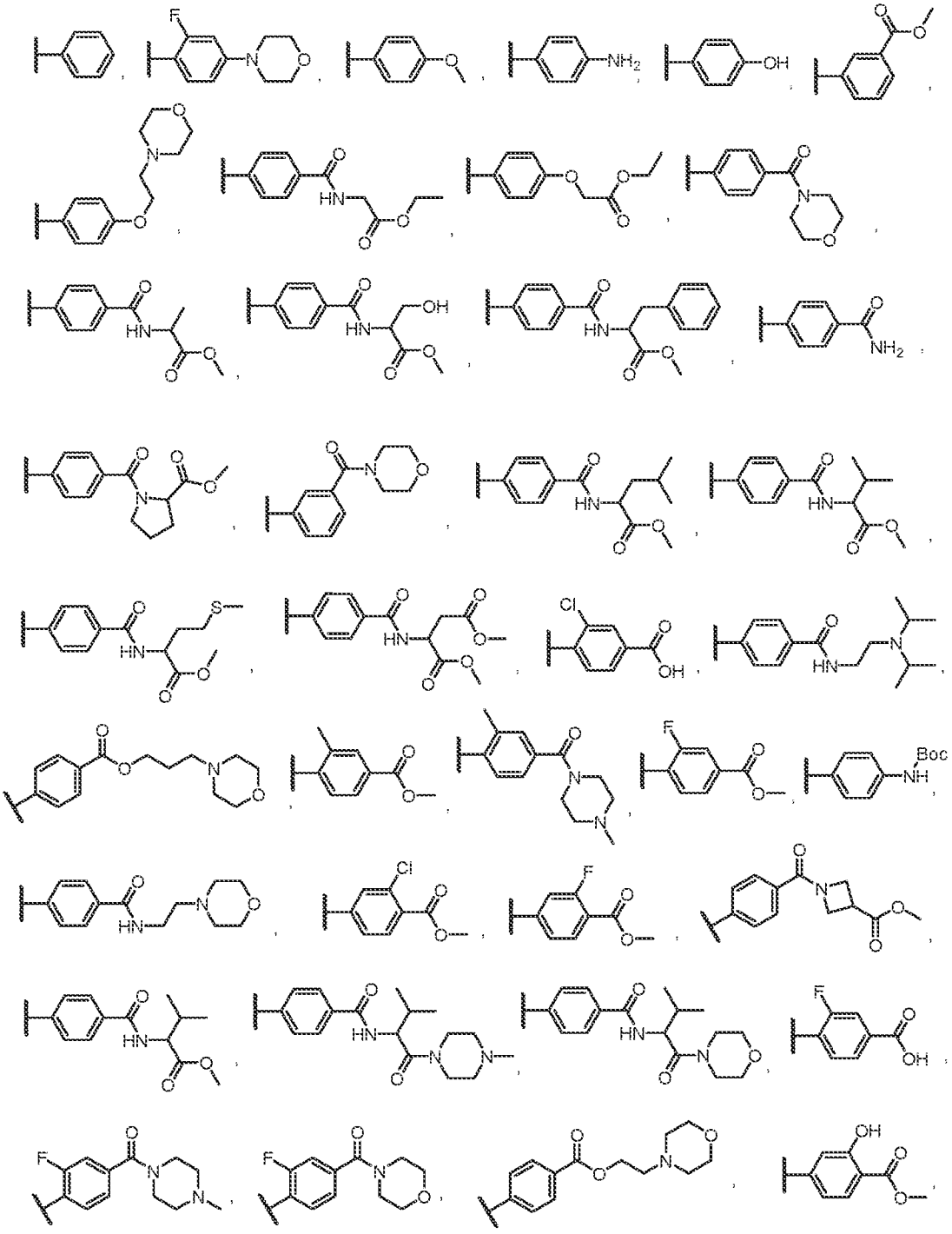
[00373] Clause 97. The compound of clause 96, wherein Y^2 and Y^3 are each CR^{14}.

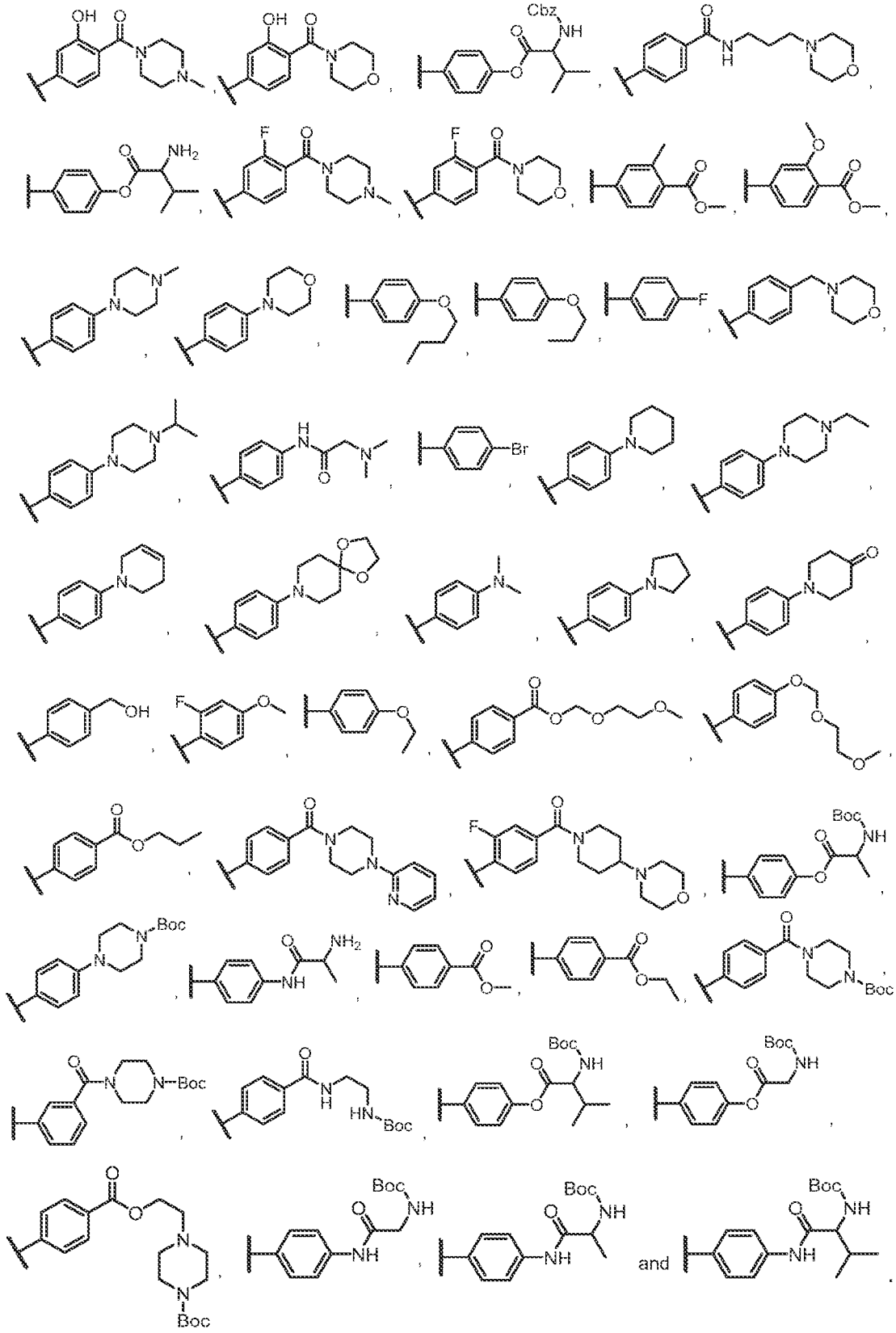
[00374] Clause 98. The compound of clause 96 or 97, wherein:

each R^{14} is independently selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, -$C(O)R^{42f}$, -$OC(O)R^{42g}$, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy; and

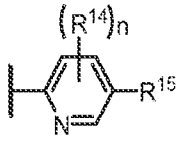
R^{15} is selected from H, halogen, -$OC(O)R^{42a}$, -$C(O)R^{42b}$, -$C(O)NHR^{42c}$, R^{42d} or -OR^{42e}, wherein R^{42a} to R^{42g} are independently selected from -OH, optionally substituted amino, optionally substituted (C_1-C_6)alkyl, optionally substituted cycloalkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted heterocycle, optionally substituted -O-(C_1-C_6)alkyl-heterocycle, and amino acid.

[00375] Clause 99. The compound of any one of clauses 96 to 98, wherein R^6 is selected from:

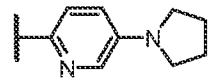
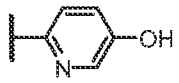
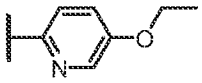
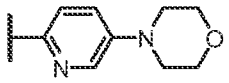


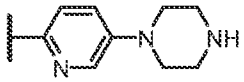
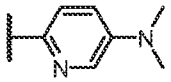
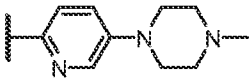
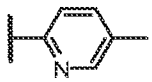


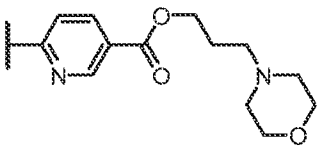
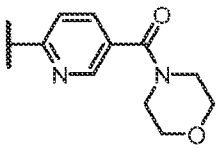
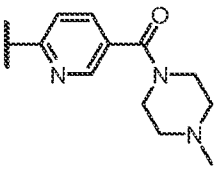
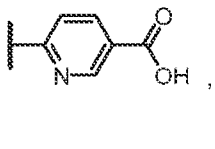
and

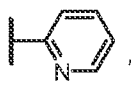
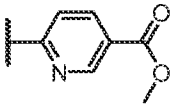
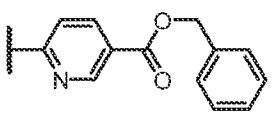
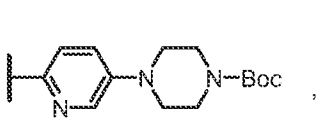
[00376] Clause 100. The compound of clause 89, wherein R^6 is  and n is 0 to 3.

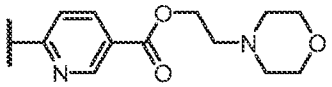
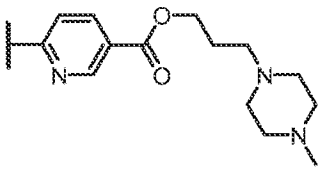
[00377] Clause 101. The compound of clause 100, wherein R^6 is selected from:

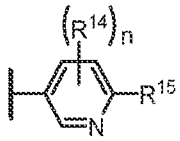
 ,  ,  ,  ,

 ,  ,  ,  ,

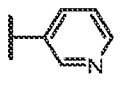
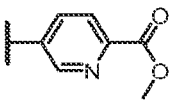
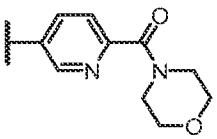
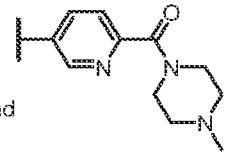
 ,  ,  ,  ,

 ,  ,  ,  ,

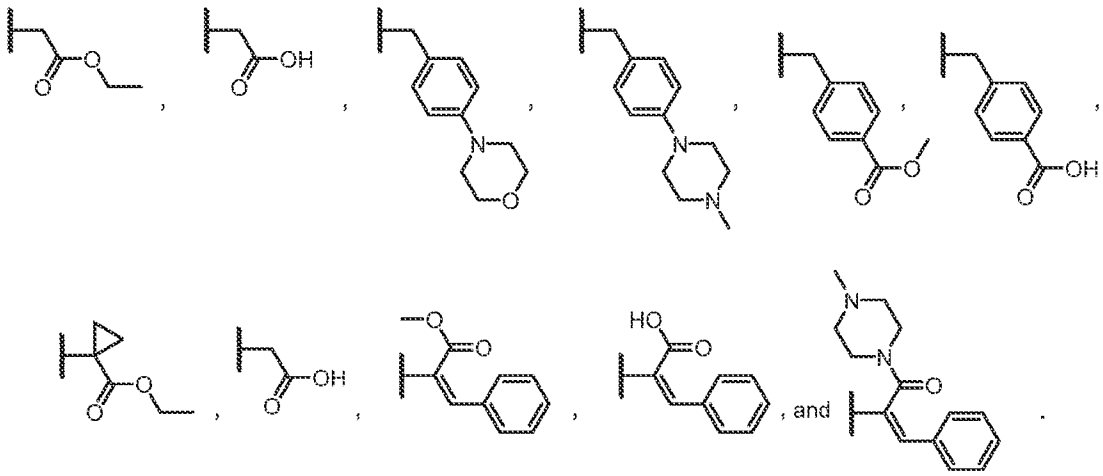
 and  .

[00378] Clause 102. The compound of clause 89, wherein R^6 is  and n is 0 to 3.

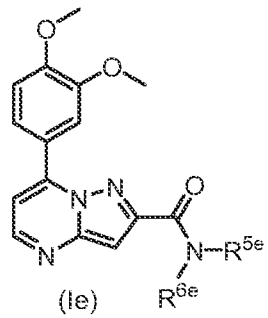
[00379] Clause 103. The compound of clause 102, wherein R^6 is selected from:

 ,  ,  , and  .

[00380] Clause 104. The compound of any one of clauses 65 to 74, wherein R^5 is H or Me, and R^6 is selected from:



[00381] Clause 105. The compound of any one of clauses 65-104, wherein the compound is of formula (Ie):



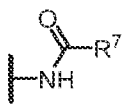
(Ie)

wherein:

R^{5e} and R^{6e} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

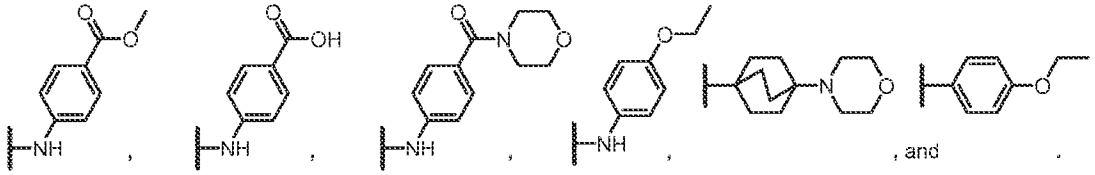
or R^{5e} and R^{6e} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle.

[00382] Clause 106. The compound of any one of clause 65 to 73, wherein any of R^4-R^{4d} is



[00383] Clause 107. The compound of clause 106, wherein R^7 is selected from optionally substituted N-anilino, optionally substituted phenyl and optionally substituted bicyclic carbocycle.

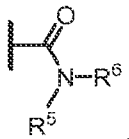
[00384] Clause 108. The compound of clause 106, wherein R^7 is selected from:



[00385] Clause 109. The compound of any one of clauses 65 to 108, wherein the compound is of Table 1.

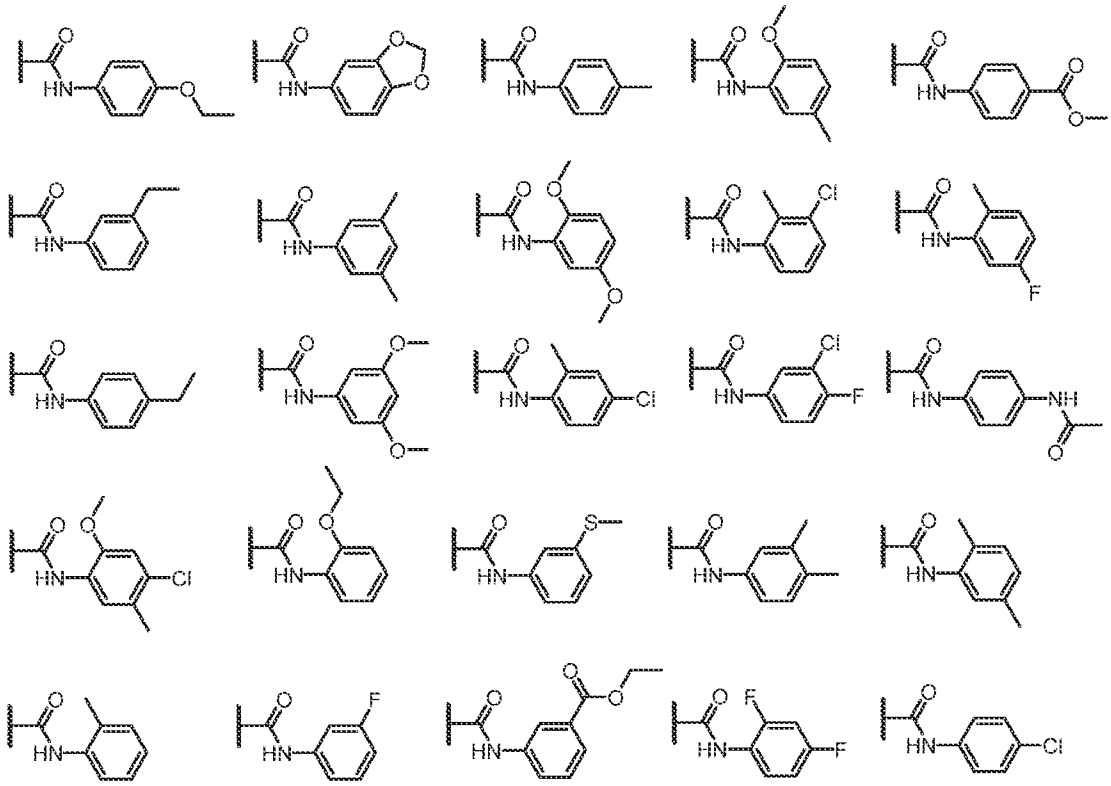
[00386] Clause 110. The compound of any one of clauses 65 to 108, wherein the compound is not a compound of Table 2.

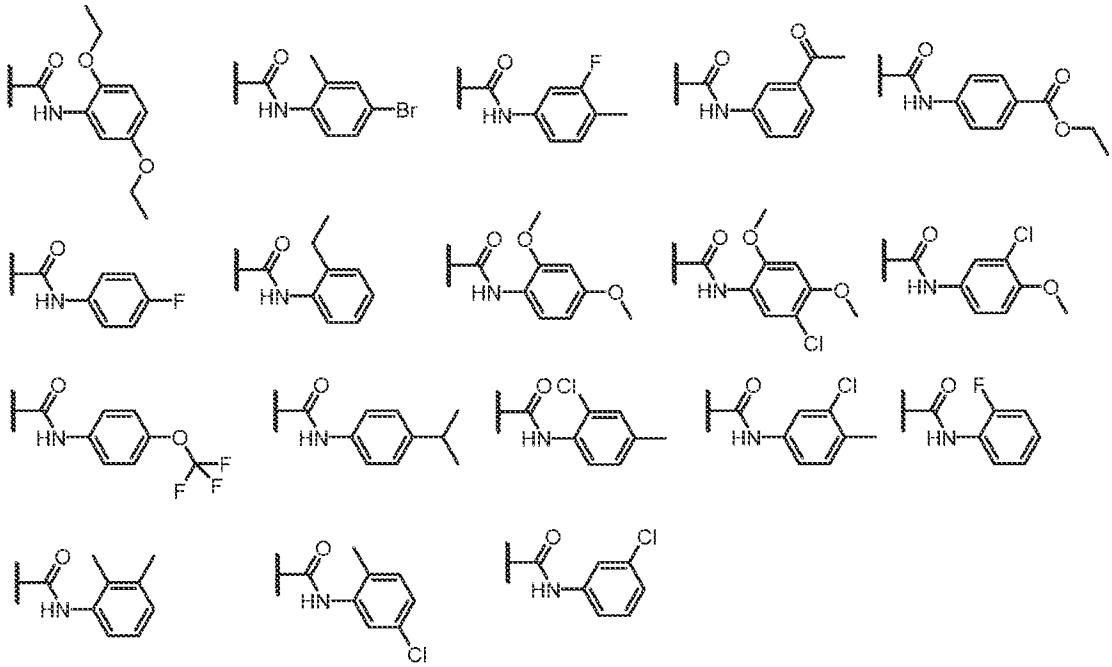
[00387] Clause 110. The compound of any one of clauses 65 to 110, wherein:



when R^1 and R^9 are H, R^4 is , R^5 is H, and R^6 is optionally substituted aryl; then R^2 is not 4-fluoro-phenyl, p-toluene, 3,5-dichloro-phenyl, or phenyl; or

when R^1 and R^9 are H, and R^4 is any one of the following:





then R^2 is not 3,4-dimethoxy-phenyl.

[00388] Clause 111. A pharmaceutical composition comprising:

a therapeutically effective amount of a compound of formula (Ia), or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, according to clause 65; and

a pharmaceutically acceptable excipient.

[00389] Clause 112. The pharmaceutical composition of clause 111, wherein the compound of formula (Ia) is a compound or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof according to any one of clauses 66 to 110.

[00390] Clause 113. The pharmaceutical composition of any one of clauses 111 to 112, wherein the composition is an ophthalmic composition, and comprises a physiologically compatible ophthalmic vehicle.

[00391] Clause 114. The pharmaceutical composition of any one of clauses 111 to 113, wherein the composition is an aqueous solution.

[00392] Clause 115. A compound for use in modulating cystic fibrosis transmembrane conductance regulator (CFTR), wherein the compound is according to any one of clauses 65 to 110.

[00393] Clause 116. A pharmaceutical composition for use in modulating CFTR, wherein the pharmaceutical composition is according to any one of clauses 111 to 114.

[00394] Clause 117. A compound for use in inhibiting phosphodiesterase 4 (PDE4), wherein the compound is according to any one of clauses 65 to 110.

[00395] Clause 118. A pharmaceutical composition for use in inhibiting PDE4, wherein the pharmaceutical composition is according to any one of clauses 111 to 114.

[00396] Clause 119. A method of modulating CFTR, the method comprising contacting a sample or biological system with an effective amount of a compound to modulate the CFTR, wherein the compound is of formula (Ia), or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, according to clause 65.

[00397] Clause 120. A method of inhibiting PDE4, the method comprising contacting a sample or biological system with an effective amount of a PDE inhibiting compound to inhibit PDE4, wherein the compound is of formula (Ia), or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, according to clause 65.

[00398] Clause 121. The method of clause 119 or 120, wherein the sample is *in vitro*.

[00399] Clause 122. The method of clause 119 or 120, wherein the biological system is in vivo.

[00400] As described herein, the text refers to various embodiments of the present compounds, compositions, and methods. The various embodiments described are meant to provide a variety of illustrative examples and should not be construed as descriptions of alternative species. Rather, it should be noted that the descriptions of various embodiments provided herein may be of overlapping scope. The embodiments discussed herein are merely illustrative and are not meant to limit the scope of the present technology.

6. EXAMPLES

[00401] The following examples are offered to illustrate the present disclosure and are not to be construed in any way as limiting the scope of the present technology. Any methods that are functionally equivalent are within the scope of the present technology. Various modifications of the present technology in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications fall within the scope of the appended claims.

[00402] Unless otherwise stated, all temperatures are in degrees Celsius. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental errors and deviation should be allowed for.

[00403] All experiments conformed to the ethical guidelines for investigation in conscious animals and in full compliance with the central Israeli animal care commission.

[00404] In the examples below, if an abbreviation is not defined, it has its generally accepted meaning.

aq.	=	aqueous
LC-MS	=	liquid chromatography-mass spectrometry
MS	=	mass spectrometry
THF	=	tetrahydrofuran

$NaHCO_3$	=	sodium bicarbonate
Cs_2CO_3 =	cesium carbonate	
NaH	=	sodium hydride
o/n	=	overnight
HATU	=	1-[Bis(dimethylamino)methylene]-1H-1,2,3-trI zolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
r.t.	=	room temperature
LAH	=	lithium aluminum hydride
DCM	=	dichloromethane
DMF	=	dimethylformamide
DMSO	=	dimethyl sulfoxide
DIEA	=	diisopropylethylamine
equiv.	=	equivalent
EtOAc or EA	=	ethyl acetate
EtOH	=	ethanol
EDCI	=	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
g	=	gram
h	=	hours
HCl	=	hydrochloric acid
HPLC	=	high-performance liquid chromatography
HOAc	=	acetic acid
HBTU	=	O-benzotriazole-N,N,N`,N`-tetramethyluronium-hexafluorophosphate
M	=	molar
MeOH	=	methanol
mg	=	milligrams
mL	=	milliliters
mmol	=	millimols
mp	=	melting point
m/z	=	mass to charge ratio
NaCl	=	sodium chloride
Na_2CO_3 =	sodium carbonate	
NMR	=	nuclear magnetic resonance
NaOH	=	sodium hydroxide
Na_2SO_4 =	sodium sulfate	
ppm	=	parts per million
TFA	=	trifluoroacetic acid

TLC	=	thin layer chromatography
SCOP	=	scopolamine
TsOH	=	p-Toluenesulfonic acid
UV	=	ultraviolet
wt %	=	weight percent
µM	=	micromolar

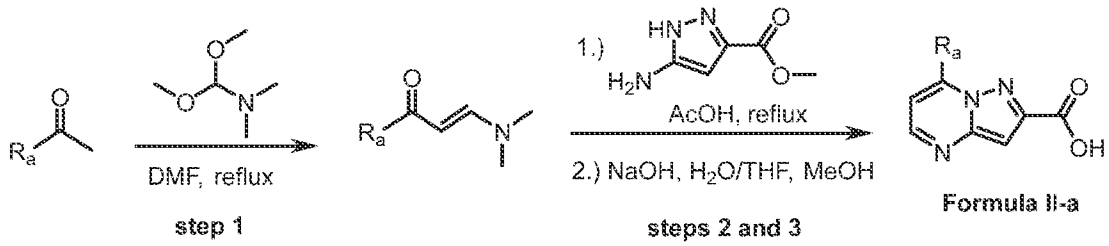
General Synthetic Methods

[00405] Final compounds were confirmed by HPLC/MS analysis and determined to be >90% pure by weight. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (residual internal standard $CHCl_3$ = δ 7.26), DMSO-d_6 (residual internal standard CD_3SOCD_2H = δ 2.50), methanol-d_4 (residual internal standard CD_2HOD = δ 3.20), or acetone-d_6 (residual internal standard CD_3COCD_2H = δ 2.05). The chemical shifts (δ) reported are given in parts per million (ppm) and the coupling constants (J) are in Hertz (Hz). The spin multiplicities are reported as s = singlet, bs = broad singlet, bm = broad multiplet, d = doublet, t = triplet, q = quartet, p = pentuplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, tt = triplet of triplet, and m = multiplet.

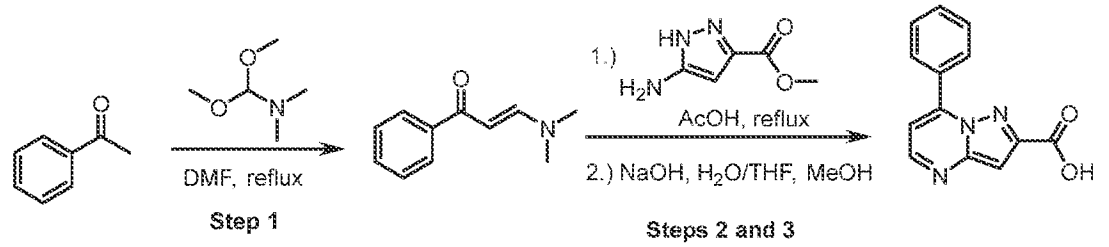
[00406] HPLC-MS analysis was carried out with gradient elution. Medium pressure liquid chromatography (MPLC) was performed with silica gel columns in both the normal phase and reverse phase.

Example 1 – Synthesis of Common Intermediates

Method A – Synthesis of 7-substituted pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (formula II-a)



Synthesis of 7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxylic acid



Step 1

[00407] Acetophenone (0.29 mL, 2.5 mmol) and DMF-DMA (1.33 mL, 10 mmol) were combined in DMF (2.5 mL) and heated to reflux for 17 hr. The reaction mixture was extracted by DCM and aq. NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The mixture was extracted by EA and aq. NH_4Cl to give (E)-3-(dimethylamino)-1-phenylprop-2-en-1-one (193 mg, 43%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.85 (m, 2H), 7.72 (d, J = 12.3 Hz, 1H), 7.55 – 7.38 (m, 3H), 5.83 (d, J = 12.3 Hz, 1H), 3.15 (s, 3H), 2.91 (s, 3H).

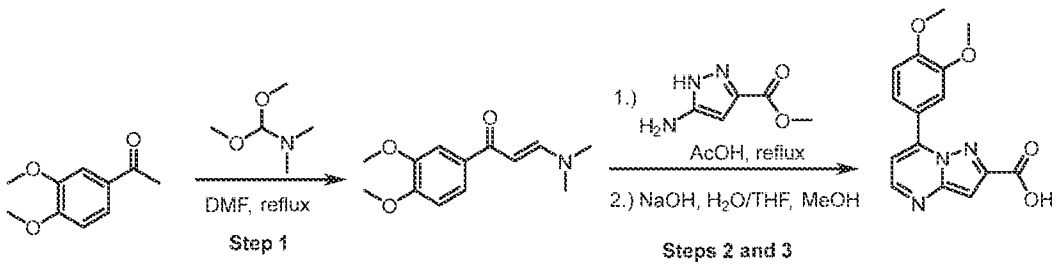
Step 2

[00408] (E)-3-(dimethylamino)-1-phenylprop-2-en-1-one (190 mg, 1.08 mmol) and methyl 5-amino-1H-pyrazole-3-carboxylate (152 mg, 1.08 mmol) were dissolved in acetic acid (5.4 mL) and heated to reflux for 2.5 hr. The reaction mixture was extracted by DCM and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The reaction mixture was purified by MPLC. The crude mixture was solidified by using DCM and hexane to give methyl 7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxylate (87.8 mg, 32%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 4.3 Hz, 1H), 8.14 – 8.04 (m, 2H), 7.71 – 7.61 (m, 3H), 7.41 (d, J = 4.3 Hz, 1H), 7.31 (s, 1H), 3.90 (s, 3H).

Step 3

[00409] Methyl 7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxylate (87 mg, 0.34 mmol) was dissolved in H_2O/THF/MeOH (1.4/2.2/1.1 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 0.68 mL) and stirred at 60 °C for 2 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the precipitated crystals were filtered out by using H_2O to give 7-phenylpyrazolo[1,5-a]pyrimidine-2-carboxylic acid (65.5 mg, 80%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 13.3 (bs, 1H), 8.72 (d, J = 4.3 Hz, 1H), 8.16 – 8.05 (m, 2H), 7.73 – 7.60 (m, 3H), 7.39 (d, J = 4.3 Hz, 1H), 7.23 (s, 1H).

Synthesis of 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



Step 1

[00410] 3',4'-Dimethoxyacetophenone (1 g, 5.55 mmol) and DMF-DMA (2.95 mL, 22.2 mmol) were combined in DMF (5.55 mL) and heated to reflux for 18 hr. The mixture was extracted by DCM

and aq. NH_4Cl. The reaction mixture was solidified by using diethyl ether to give (E)-1-(3,4-dimethoxyphenyl)-3-(dimethylamino)prop-2-en-1-one (797 mg, 61%) as an orange solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 12.4 Hz, 1H), 7.54 (dd, J = 8.4, 2.0 Hz, 1H), 7.45-7.44 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.82 (d, J = 12.4 Hz, 1H), 3.82 – 3.80 (m, 6H), 3.13 (s, 3H), 2.91 (s, 3H).

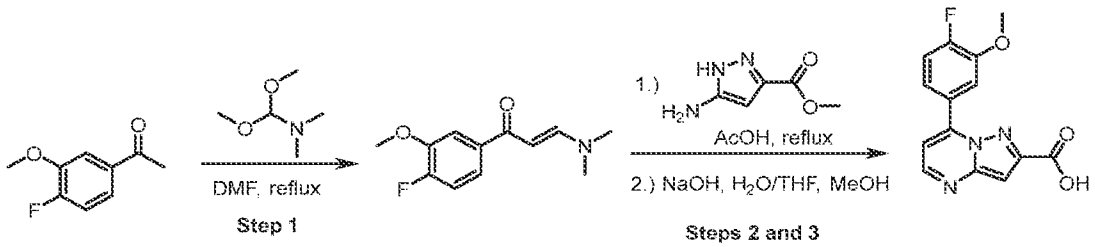
Step 2

[00411] (E)-1-(3,4-dimethoxyphenyl)-3-(dimethylamino)prop-2-en-1-one (790 mg, 3.35 mmol) and methyl 5-amino-1H-pyrazole-3-carboxylate (473 mg, 3.35 mmol) were dissolved in acetic acid (15 mL) and heated to reflux for 2 hr. After evaporating acetic acid, the mixture was solidified by using diethyl ether to give Methyl 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (919 mg, 88%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.4 Hz, 1H), 7.87 (dd, J = 8.6 Hz, 2.4 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.25 (s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H).

Step 3

[00412] Methyl 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (915 mg, 2.92 mmol) was dissolved in H_2O/THF/MeOH (12/20/10 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 5.84 mL) and stirred at 60 °C for 2 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the precipitated crystals were filtered out by using H_2O to give 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (980 mg, >99%) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 13.35 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 7.90 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 4.4 Hz, 1H), 7.22 – 7.20 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H).

Synthesis of 7-(4-fluoro-3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



Step 1

[00413] 1-(4-Fluoro-3-methoxyphenyl)ethan-1-one (500 mg, 2.97 mmol) and DMF-DMA (1.58 mL, 11.9 mmol) were combined in DMF (2.97 mL) and heated to reflux for 21 hr. The mixture was extracted by DCM and aq. NH_4Cl. The reaction mixture was solidified by using DCM and hexane to give (E)-3-(dimethylamino)-1-(4-fluoro-3-methoxyphenyl)prop-2-en-1-one (516 mg, 77%) as an orange solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 12.2 Hz, 1H), 7.60 (dd, J = 8.7, 2.0 Hz,

1H), 7.56 – 7.49 (m, 1H), 7.29 – 7.20 (m, 1H), 5.82 (d, J = 12.2 Hz, 1H), 3.89 (s, 3H), 3.15 (s, 3H), 2.92 (s, 3H).

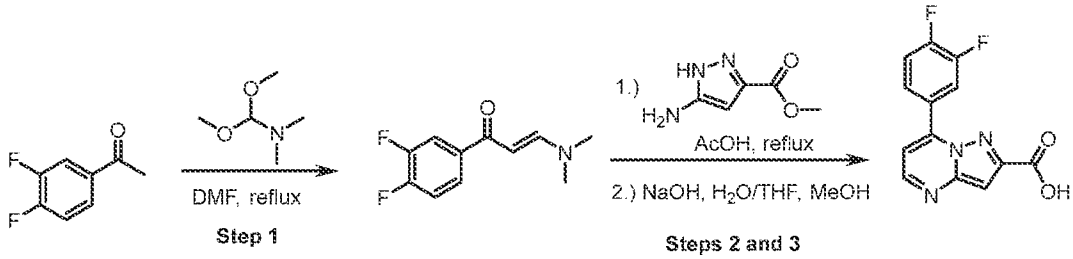
Step 2

[00414] (E)-3-(dimethylamino)-1-(4-fluoro-3-methoxyphenyl)prop-2-en-1-one (515 mg, 2.3 mmol) and methyl 5-amino-1H-pyrazole-3-carboxylate (325 mg, 2.3 mmol) were dissolved in acetic acid (12 mL) and heated to reflux for 2 hr. The reaction mixture was extracted by DCM and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was solidified by using DCM and hexane to give methyl 7-(4-fluoro-3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (1950 mg, >99%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 4.4 Hz, 1H), 7.92 (dd, J = 8.4, 2.1 Hz, 1H), 7.80 – 7.74 (m, 1H), 7.55 – 7.45 (m, 2H), 7.31 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H).

Step 3

[00415] Methyl 7-(4-fluoro-3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (693 mg, 2.3 mmol) was dissolved in H_2O/THF/MeOH (9/15/8 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 4.6 mL) and stirred at 60 °C for 4 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the precipitated crystals were filtered out by using H_2O to give 7-(4-fluoro-3-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (521 mg, 79%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.73 (d, J = 4.4 Hz, 1H), 7.93 (dd, J = 8.4, 2.1 Hz, 1H), 7.83 – 7.76 (m, 1H), 7.56 – 7.42 (m, 2H), 7.23 (s, 1H), 3.94 (s, 3H).

Synthesis of 7-(3,4-difluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



Step 1

[00416] 1-(3,4-difluorophenyl)ethan-1-one (1000 mg, 6.41 mmol) and DMF-DMA (3.40 mL, 25.62 mmol) were combined in DMF (3 mL) and heated to reflux for 22 hr. The mixture was extracted by DCM and aq. NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give (E)-1-(3,4-difluorophenyl)-3-(dimethylamino)prop-2-en-1-one (1275.4 mg, >99%) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.88 (m, 1H), 7.82 – 7.77 (m, 1H), 7.74 (d, J = 12.2 Hz, 1H), 7.53 – 7.45 (m, 1H), 5.85 (d, J = 12.2 Hz, 1H), 3.15 (s, 3H), 2.93 (s, 3H).

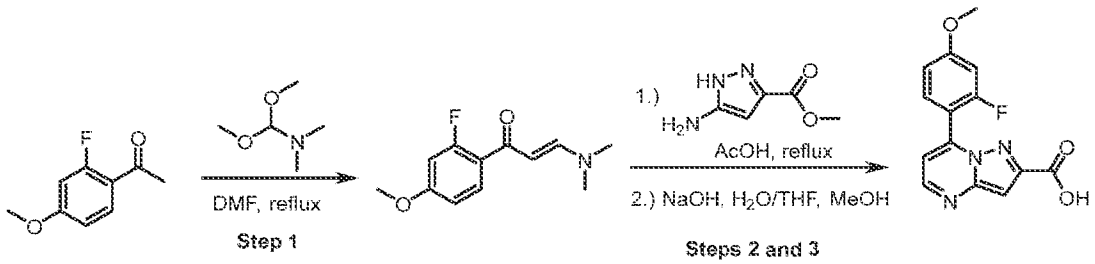
Step 2

[00417] (E)-1-(3,4-difluorophenyl)-3-(dimethylamino)prop-2-en-1-one (1275 mg, 6.04 mmol) and methyl 5-amino-1H-pyrazole-3-carboxylate (852 mg, 6.04 mmol) were dissolved in acetic acid (30 mL) and heated to reflux for 1 hr. The reaction mixture was extracted by DCM and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was solidified by using DCM and hexane to give methyl 7-(3,4-difluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (1188 mg, 68%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J = 4.4 Hz, 1H), 8.32 – 8.23 (m, 1H), 8.05 – 7.97 (m, 1H), 7.80 – 7.70 (m, 1H), 7.48 (d, J = 4.4 Hz, 1H), 7.33 (s, 1H), 3.90 (s, 3H).

Step 3

[00418] Methyl 7-(3,4-difluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (1188 mg, 4.11 mmol) was dissolved in H_2O/THF/MeOH (16/20/10 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 8.22 mL) and stirred at 60 °C for 2 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the precipitated crystals were filtered out by using H_2O to give 7-(3,4-difluorophenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (280 mg, 25%) as a pale orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.45 (s, 1H), 8.74 (d, J = 4.4 Hz, 1H), 8.36 – 8.27 (m, 1H), 8.09 – 8.01 (m, 1H), 7.79 – 7.70 (m, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.25 (s, 1H).

Synthesis of 7-(2-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



Step 1

[00419] 1-(2-fluoro-4-methoxyphenyl)ethan-1-one (1000 mg, 5.95 mmol) and DMF-DMA (3.2 mL, 23.8 mmol) were combined in DMF (6 mL) and heated to reflux for 18 hr. The mixture was extracted by DCM and aq. NH_4Cl. After evaporating DCM, the mixture was extracted by EA and aq. NH_4Cl. The reaction mixture was solidified by using diethyl ether to give (E)-3-(dimethylamino)-1-(2-fluoro-4-methoxyphenyl)prop-2-en-1-one (1057 mg, 80%) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 – 7.57 (m, 2H), 6.87 – 6.77 (m, 2H), 6.99 (d, J = 12.2 Hz, 1H), 3.80 (s, 3H), 3.12 (s, 3H), 2.84 (s, 3H).

Step 2

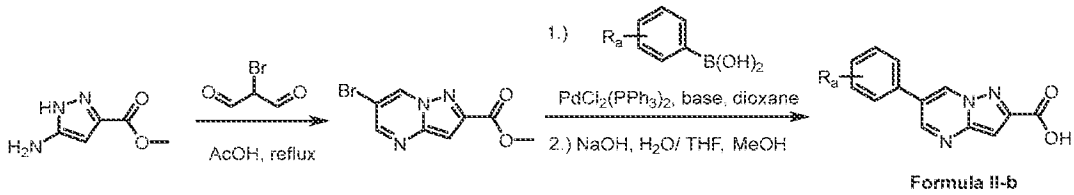
[00420] (E)-3-(dimethylamino)-1-(2-fluoro-4-methoxyphenyl)prop-2-en-1-one (1057 mg, 4.74 mmol) and methyl 5-amino-1H-pyrazole-3-carboxylate (668 mg, 4.74 mmol) were dissolved in acetic

acid (24 mL) and heated to reflux for 8 hr. After evaporating acetic acid, the mixture was extracted by EA and aq. NaOH to give methyl 7-(2-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (972 mg, 68%) as a pale orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 4.3 Hz, 1H), 7.77 (t, J = 8.5 Hz, 1H), 7.32 (dd, J = 4.3, 0.7 Hz, 1H), 7.30 (s, 1H), 7.14 (dd, J = 12.4, 2.4 Hz, 1H), 7.04 (dd, J = 8.7, 2.5 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H).

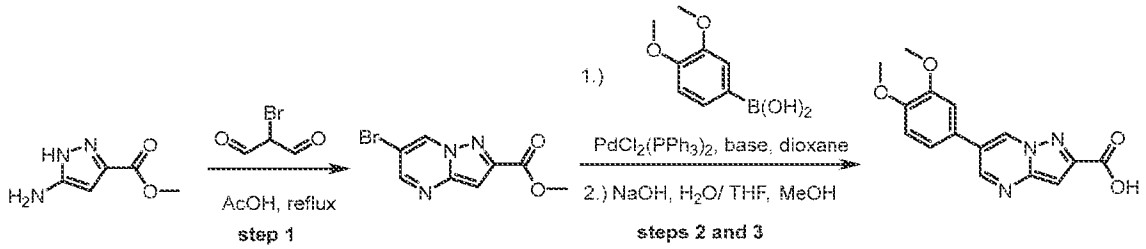
Step 3

[00421] Methyl 7-(2-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylate (970 mg, 3.22 mmol) was dissolved in H_2O/THF/MeOH (12/20/10 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 6.44 mL) and stirred at 60 °C for 4 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the precipitated crystals were filtered out by using H_2O to give 7-(2-fluoro-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (790 mg, 85%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 8.70 (d, J = 4.3 Hz, 1H), 7.78 (t, J = 8.5 Hz, 1H), 7.29 (dd, J = 4.2, 0.7 Hz, 1H), 7.22 (s, 1H), 7.13 (dd, J = 12.4, 2.4 Hz, 1H), 7.03 (dd, J = 8.7, 2.5 Hz, 1H), 3.89 (s, 3H).

Method B – Synthesis of 6-substituted pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (formula II-b)



Synthesis of 6-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



Step 1

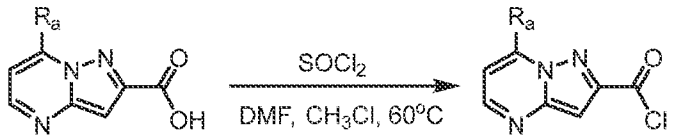
[00422] 2-Bromomalonaldehyde (200 mg, 1.32 mmol) and methyl 5-amino-1H-pyrazole-3-carboxylate (187 mg, 1.32 mmol) were dissolved in acetic acid (13 mL) and heated to reflux for 22 hr. After evaporating acetic acid, the mixture was extracted by DCM and aq. HCl. The reaction mixture was purified by MPLC to give a product, methyl 6-bromopyrazolo[1,5-a]pyrimidine-2-carboxylate

(138 mg, 41%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (dd, J = 2.2, 0.9 Hz, 1H), 8.77 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 0.8 Hz, 1H), 3.91 (s, 3H).

Step 2 and 3

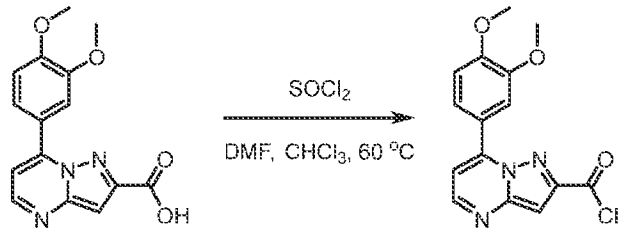
[00423] methyl 6-bromopyrazolo[1,5-a]pyrimidine-2-carboxylate (130 mg, 0.508 mmol) and $PdCl_2(PPh_3)_2$ (4 mg, 0.01 mmol) were purged in vacuo. After 40 min, the reagents were dissolved in dioxane (5 mL). To a solution, sodium carbonate (2 M, 2.29 mL) in water was added and heated to 90 °C. After 0.5 hr, a solution of 3,4-dimethoxyphenylboronic acid in dioxane (2 mL) was added and stirred for 1hr. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The reaction mixture was dissolved in H_2O/THF/MeOH (2/4/2 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 1.1 mL) and stirred at 60 °C for 4 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the precipitated crystals were filtered out by using H_2O to give 6-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (90 mg, 59%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 9.54 (s, 1H), 9.08 (d, J = 2.2 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.16 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H).

Method C – Synthesis of 7-substituted pyrazolo[1,5-a]pyrimidine-2-carbonyl chloride (formula II-c)



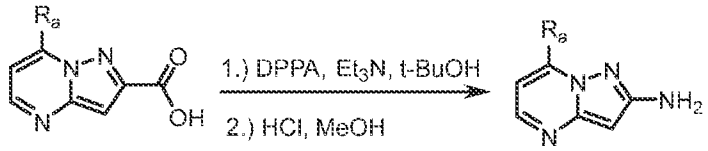
Formula II-c

Synthesis of 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl chloride



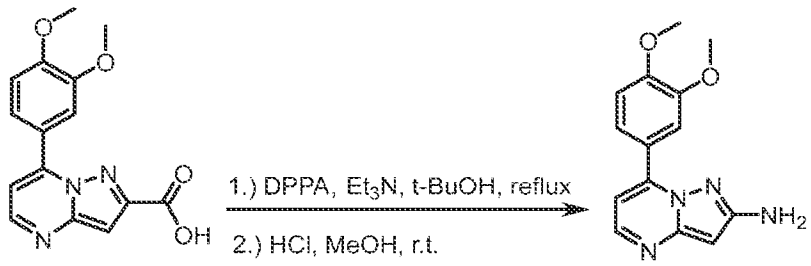
[00424] To a solution of 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (70 mg, 0.23 mmol) in chloroform (2.3 mL), DMF (catalytic amount) and $SOCl_2$ (0.084mL, 1.15 mmol) were added and stirred at 60 °C for 2 hr. The mixture was concentrated and used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, J = 4.4 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.45 (d, J = 4.4 Hz, 1H), 7.24 – 7.16 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H).

Method D – Synthesis of 7-substituted pyrazolo[1,5-a]pyrimidin-2-amine (formula II-d)



Formula II-d

Synthesis of 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-amine



Step 1

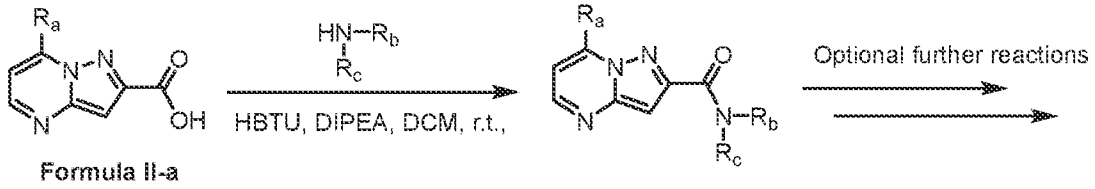
[00425] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (1 g, 3.34 mmol), DPPA (0.79 mL, 3.68 mmol), TEA (5.17 mL, 3.68 mmol) were combined in t-BuOH (0.2 M, 15 mL) and heated to reflux for 18.5 hr. After evaporation, the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The mixture was purified by MPLC. The crude mixture was solidified by using DCM and hexane to give a product, tert-butyl (7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)carbamate (260 mg, 21%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.45 (d, J = 4.6 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.74 (dd, J = 8.5, 2.2 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.71 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 1.49 (s, 9H).

Step 2

[00426] Tert-Butyl (7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)carbamate (250 mg, 0.675 mmol) was dissolved in methanol (6 mL), then hydrochloride (4 N, 3 mL) in dioxane was added at r.t.. After 16.5 hr, the mixture was basified by adding 1 N NaOH and extracted by DCM. The mixture was purified by MPLC. The crude mixture was solidified by using DCM and hexane to give a product 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-amine (157 mg, 86%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 4.6 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.13 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 4.6 Hz, 1H), 5.76 (s, 1H), 5.70 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H).

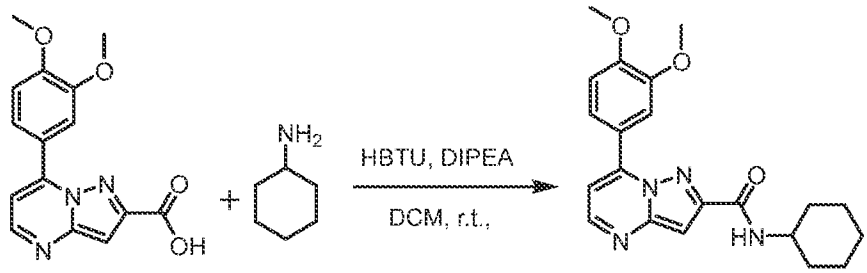
Example 2 – Synthesis of Compounds of Formulae (Ia)-(Ic)

General Method A



Formula II-a

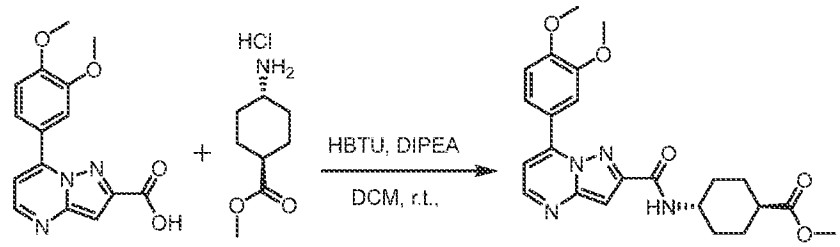
Synthesis of Compound 2



Compound 2

[00427] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (50 mg, 0.17 mmol), cyclohexylamine (0.022 mL, 0.18 mmol), HBTU (70 mg, 0.18 mmol), diisopropylethylamine (0.057 mL, 0.33 mmol) were combined in DCM. After stirring for 1 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 2, N-cyclohexyl-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (34.8 mg, 55% yield) as a white solid.

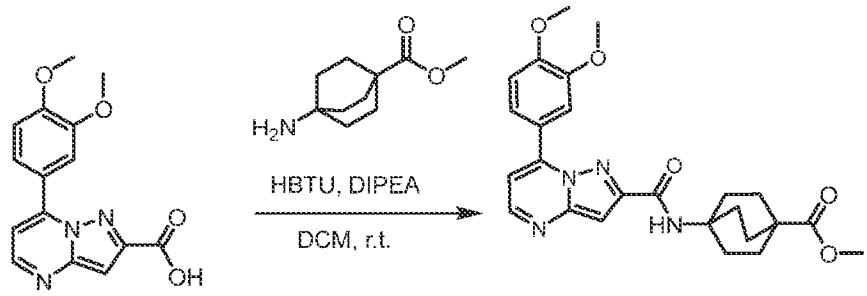
Synthesis of Compound 10



Compound 10

[00428] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (100 mg, 0.33 mmol), methyl trans-4-aminocyclohexanecarboxylate hydrochloride (71.3 mg, 0.37 mmol), HBTU (140 mg, 0.37 mmol), diisopropylethylamine (0.17 mL, 1 mmol) were combined in DCM. After stirring for 1 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 10, methyl (1r,4r)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)cyclohexane-1-carboxylate (135 mg, 92% yield) as a pale yellow solid.

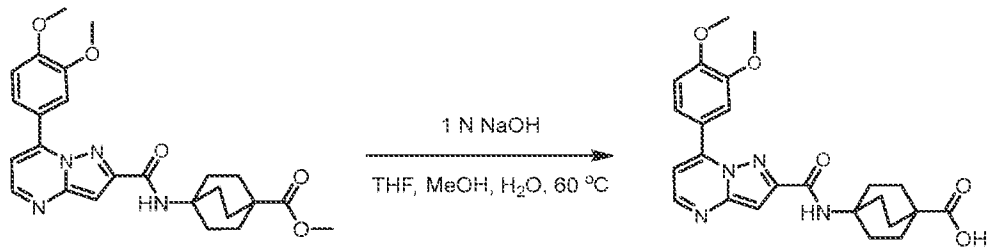
Synthesis of Compound 144



Compound 144

[00429] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (1688 mg, 5.639 mmol), 4-aminobicylo[2,2,2]octane-1-carboxylic acid methyl ester (1033.1 mg, 5.639 mmol), HBTU (2352 mg, 6.203 mmol), diisopropylethylamine (1.943 mL, 11.278 mmol) were combined in DCM. After stirring for 2 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 144, methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[2.2.2]octane-1-carboxylate (3167.6 mg, >99% yield) as a yellow solid.

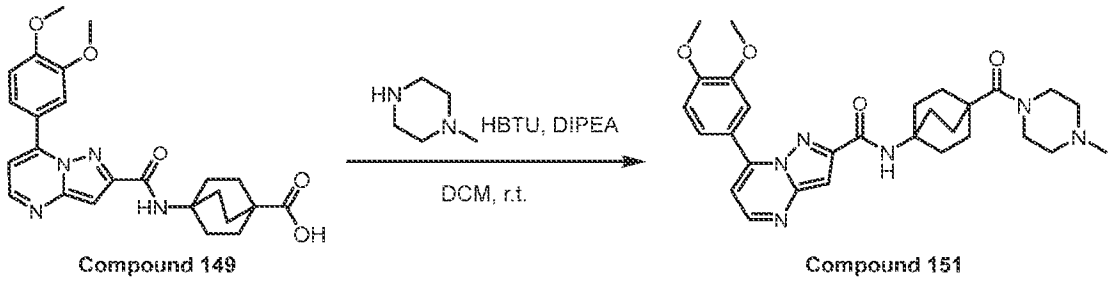
Synthesis of Compound 149



Compound 144 Compound 149

[00430] Compound 144 (3167.6 mg, 6.819 mmol) was dissolved in H_2O/THF/MeOH (27/22/11 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 13.638 mL) and stirred at 60 °C for 2 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the solid was filtered by using H_2O to give compound 149, 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[2.2.2]octane-1-carboxylic acid (1989 mg, 65%) as a pale yellow solid.

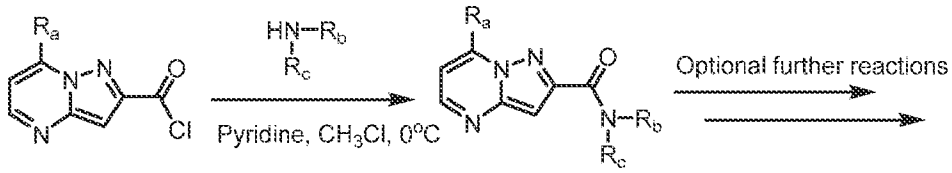
Synthesis of Compound 151



Compound 149 Compound 151

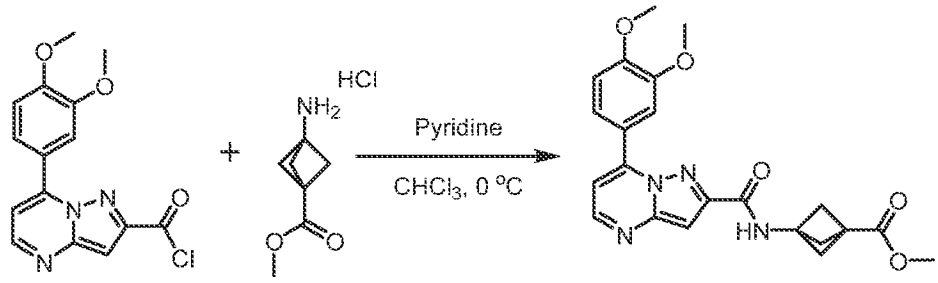
[00431] Compound 149 (1000 mg, 2.220 mmol), 1-methylpiperazine (0.271 mL, 2.442 mmol), HBTU (926 mg, 2.442 mmol), diisopropylethylamine (0.765 mL, 4.440 mmol) were combined in DCM. After stirring for 4 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$ and purified by MPLC. The crude mixture was solidified using DCM and diethyl ether to give compound 151, 7-(3,4-dimethoxyphenyl)-N-(4-(4-methylpiperazine-1-carbonyl)bicyclo[2.2.2]octan-1-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (961.6 mg, 81% yield) as a white solid.

General Method B



Formula II-c

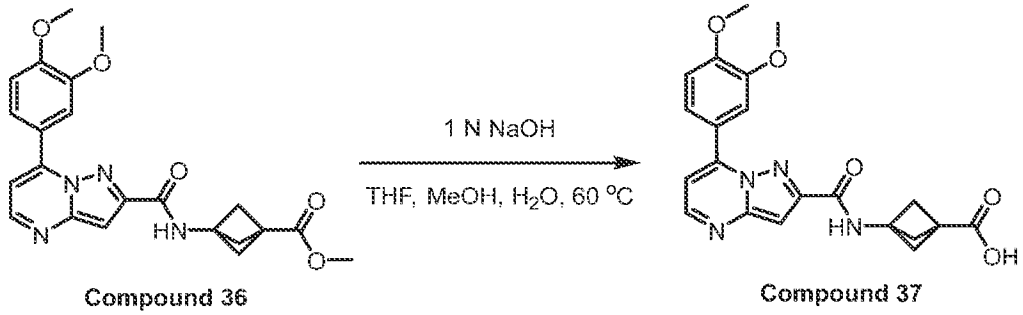
Synthesis of Compound 36



Compound 36

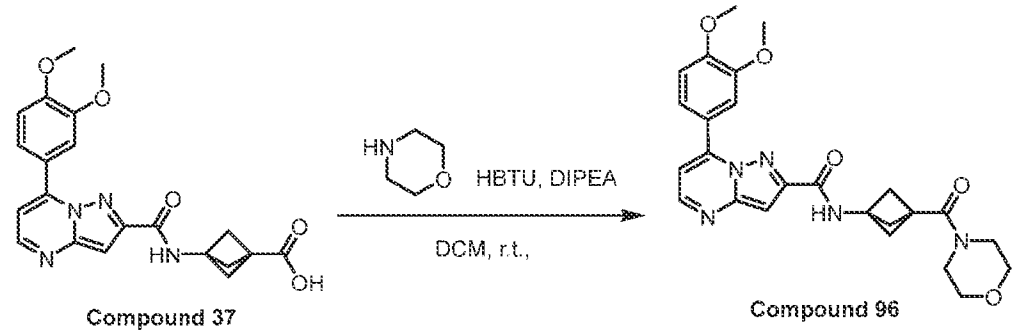
[00432] To a solution of methyl 3-aminobicyclo[1.1.1]pentane-1-carboxylate hydrochloride (47.5 mg, 0.267 mmol) and pyridine (0.136 mL, 1.67 mmol) in chloroform, 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl chloride (106 mg, 0.334 mmol) dissolved in chloroform was added dropwise and stirred for 1 hr at 0 °C. The reaction mixture was extracted by DCM and aq. NH_4Cl. The reaction mixture was purified by MPLC. The crude mixture was solidified by using DCM and hexane to give compound 36, methyl 3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[1.1.1]pentane-1-carboxylate (40.7 mg, 29%) as a white solid.

Synthesis of Compound 37



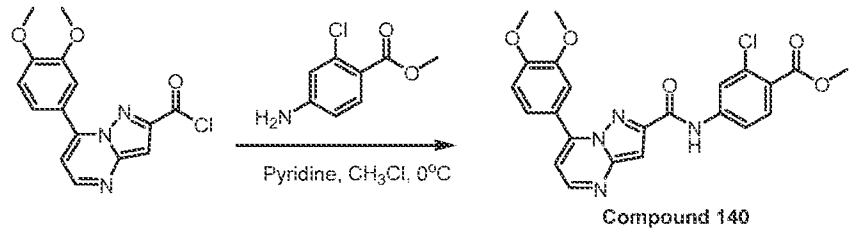
[00433] Compound 36 (60 mg, 0.142 mmol) was dissolved in H_2O/THF/MeOH (0.6/1/0.5 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 0.284 mL) and stirred at 30 °C for 2 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. The mixture was extracted by DCM and H_2O. The crude mixture was solidified by using DCM and hexane to give compound 37, 3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)bicyclo[1.1.1]pentane-1-carboxylic acid (36.8 mg, 63%) as a yellow solid.

Synthesis of Compound 96



[00434] Compound 37 (874 mg, 2.140 mmol), morpholine (0.205 mL, 2.354 mmol), HBTU (893 mg, 2.354 mmol), diisopropylethylamine (0.746 mL, 4.280 mmol) were combined in DCM. After stirring for 4 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$ and purified by MPLC. The crude mixture was solidified using DCM and n-heptane to give compound 96, 7-(3,4-dimethoxyphenyl)-N-(3-(morpholine-4-carbonyl)bicyclo[1.1.1]pentan-1-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (728.9 mg, 71% yield) as a white solid.

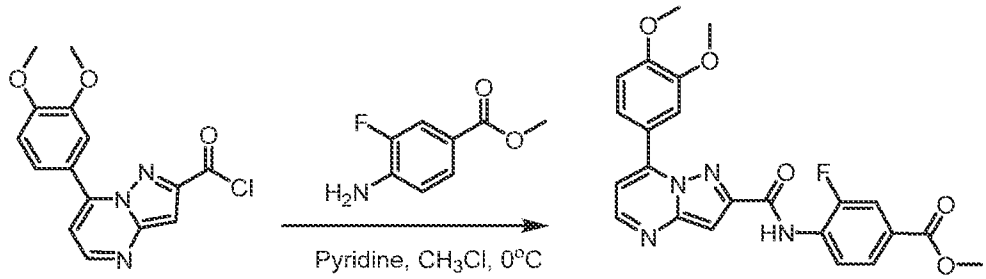
Synthesis of Compound 140



Compound 140

[00435] To a solution of methyl 4-amino-2-chlorobenzoate (278 mg, 1.5 mmol) and pyridine (0.25 mL, 3 mmol) in chloroform, 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl chloride (318 mg, 1 mmol) dissolved in chloroform was added dropwise and stirred for 17 hr at 0 °C. The reaction mixture was extracted by DCM and aq. NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The reaction mixture was purified by MPLC. The crude mixture was solidified by using DCM and hexane to give compound 140, methyl 2-chloro-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate (353 mg, 76%) as a white solid.

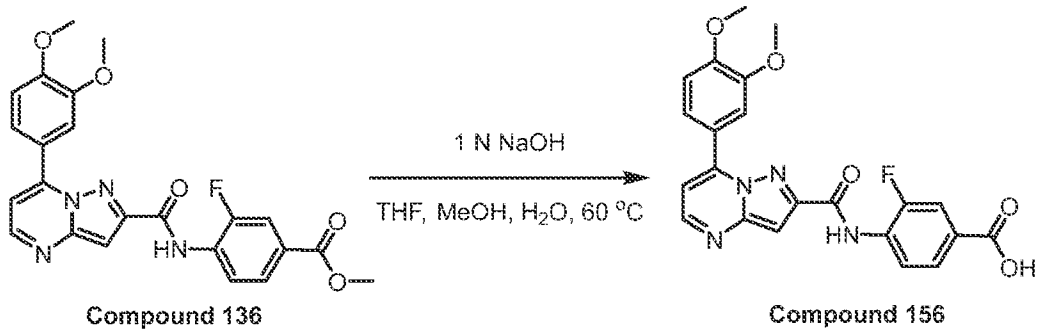
Synthesis of Compound 136



Compound 136

[00436] To a solution of methyl 4-amino-3-fluorobenzoate (339 mg, 2.01 mmol) and pyridine (0.33 mL, 4.01 mmol) in chloroform, 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl chloride (637 mg, 2.01 mmol) dissolved in chloroform was added dropwise and stirred for 2 hr at 0 °C. The reaction mixture was extracted by DCM and aq. NH_4Cl. The mixture was purified by MPLC to give compound 136, methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-fluorobenzoate (684 mg, 76%) as a white solid.

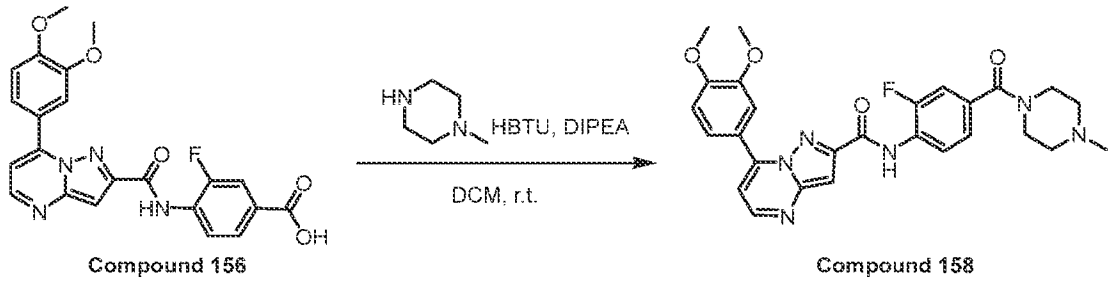
Synthesis of Compound 156



Compound 136 Compound 156

[00437] Compound 136 (550 mg, 1.22 mmol) was dissolved in H_2O/THF/MeOH (5/8/4 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 2.44 mL) and stirred at 60 °C for 30 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the solid was filtered by using H_2O. The crude mixture was purified by MPLC to give compound 156, 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)-3-fluorobenzoic acid (175 mg, 20%) as a white solid.

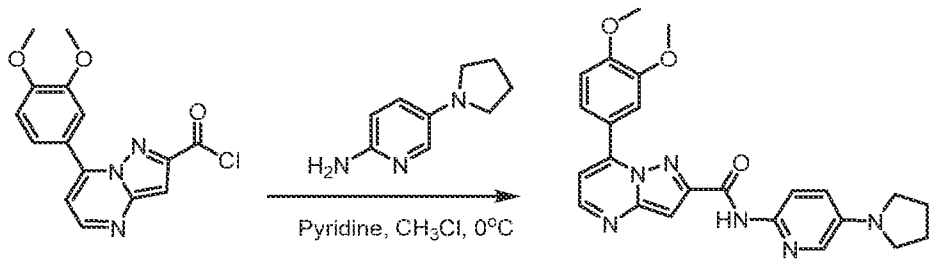
Synthesis of Compound 158



Compound 156 Compound 158

[00438] Compound 156 (80 mg, 0.183 mmol), 1-methylpiperazine (0.022 mL, 0.202 mmol), HBTU (77 mg, 0.202 mmol), diisopropylethylamine (0.063 mL, 0.366 mmol) were combined in DCM. After stirring for 1 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$ and purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 158, 7-(3,4-dimethoxyphenyl)-N-(2-fluoro-4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (43.8 mg, 46% yield) as a white solid.

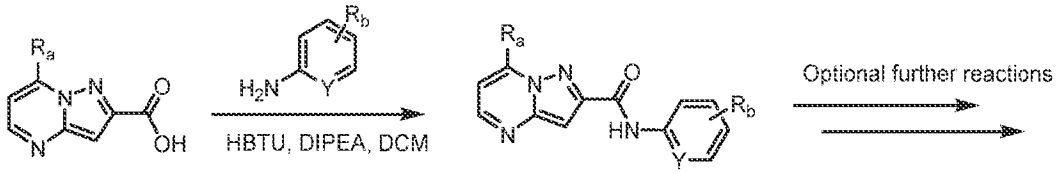
Synthesis of Compound 289



Compound 289

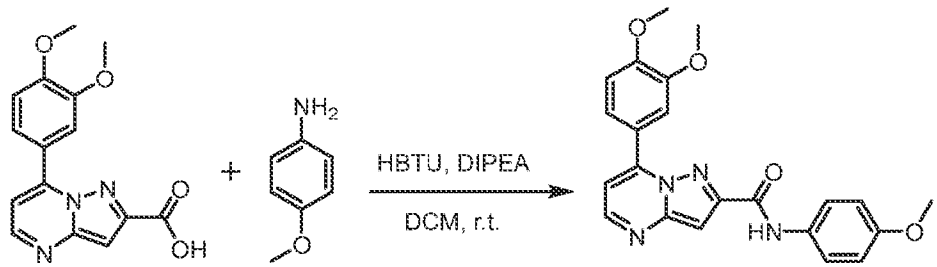
[00439] To a solution of 5-(pyrrolidin-1-yl)pyridin-2-amine (108 mg, 0.66 mmol) and pyridine (0.183 mL, 0.99 mmol) in chloroform, 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl chloride (210 mg, 0.66 mmol) dissolved in chloroform was added dropwise and stirred for 17.5 hr at 0 °C. The reaction mixture was extracted by DCM and aq. $NaHCO_3$ and purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 289, 7-(3,4-dimethoxyphenyl)-N-(5-(pyrrolidin-1-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (43.5 mg, 14%) as a brown solid.

General Method C



Formula II-a

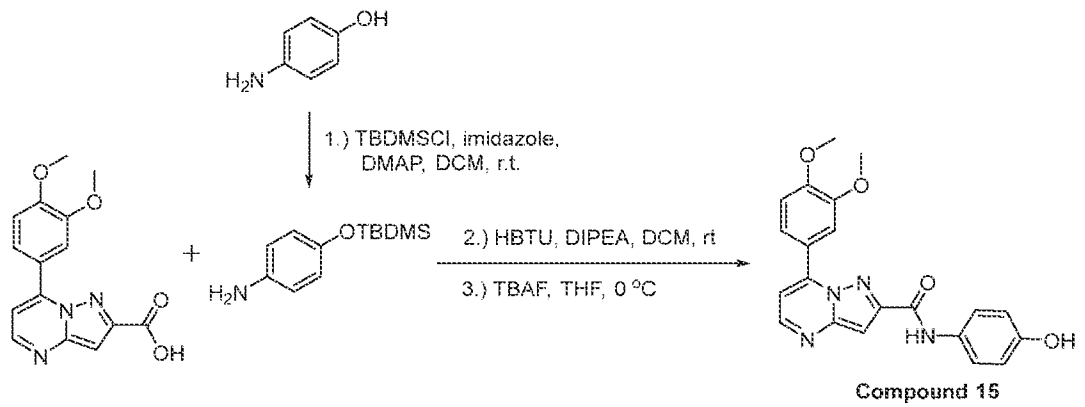
Synthesis of Compound 6



Compound 6

[00440] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (50 mg, 0.167 mmol), *p*-anisidine (22.7 mg, 0.184 mmol), HBTU (70 mg, 0.184 mmol), diisopropylethylamine (0.057 mL, 0.334 mmol) were combined in DCM. After stirring for 1 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 6, 7-(3,4-dimethoxyphenyl)-*N*-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (56.3 mg, 83% yield) as a white solid.

Synthesis of Compound 15



Compound 15

Step 1

[00441] 4-aminophenol (3 g, 27.49 mmol), imidazole (2.246 g, 32.988 mmol), DMAP (34 mg, 0.275 mmol) and TBDMSCl (4.972 g, 32.988 mmol) were combined in DCM. After stirring for 21 hr at r.t., the reaction mixture was filtered by using H_2O, and then extracted by DCM and H_2O. The crude mixture was purified by MPLC to give a product 4-((tert-butyldimethylsilyl)oxy)aniline (2709.5 mg, 44% yield) as a liquid.

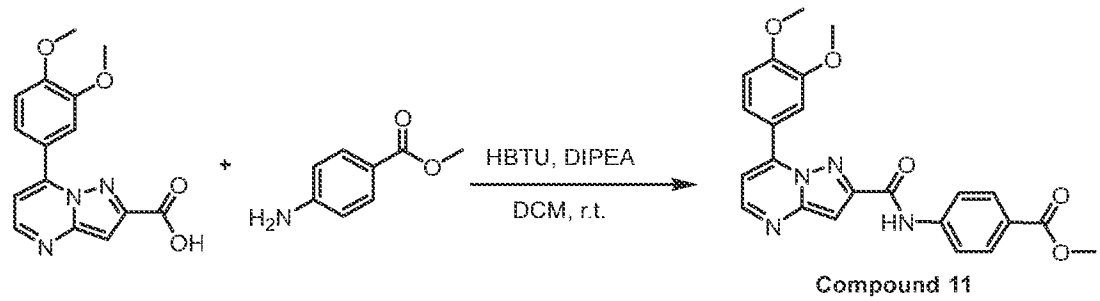
Step 2

[00442] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (3.629 g, 12.127 mmol), 4-((tert-butyldimethylsilyl)oxy)aniline (2.709 g, 12.127 mmol), HBTU (5.059 g, 13.340 mmol), diisopropylethylamine (4.214 mL, 24.454 mmol) were combined in DCM. After stirring for 5 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The mixture was purified by MPLC to give N-(4-((tert-butyldimethylsilyl)oxy)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (5409.7 mg, 88% yield) as a white solid.

Step 3

[00443] N-(4-((tert-butyldimethylsilyl)oxy)phenyl)-7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (5.409 g, 10.718 mmol) was dissolved in THF (50 mL) at 0 °C, and then TBAF (1 M, 10.718 mL) in THF was added. After 15 min, the reaction mixture was quenched by using H_2O (50 mL) and extracted by EA. The mixture was purified by MPLC. The crude mixture was solidified using DCM and diethyl ether to give compound 15, 7-(3,4-dimethoxyphenyl)-N-(4-hydroxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (2805.6 mg, 67% yield) as a white solid.

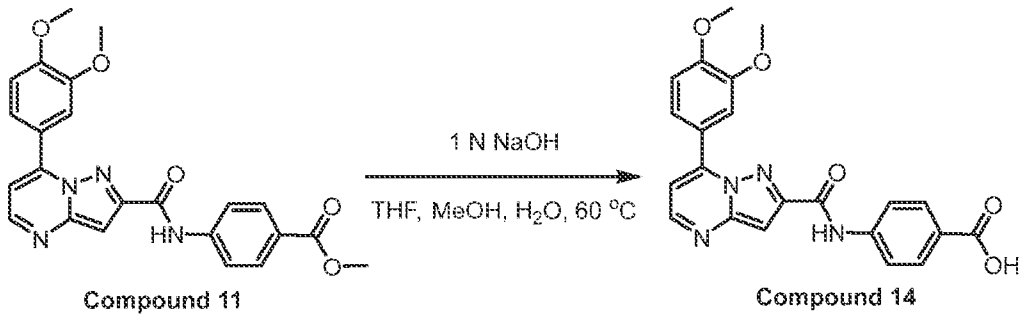
Synthesis of Compound 11



Compound 11

[00444] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (100 mg, 0.334 mmol), methyl 4-aminobenzoate (55.64 mg, 0.368 mmol), HBTU (140 mg, 0.368 mmol), diisopropylethylamine (0.114 mL, 0.668 mmol) were combined in DCM. After stirring for 1 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 11, methyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate (75 mg, 52% yield) as a pale yellow solid.

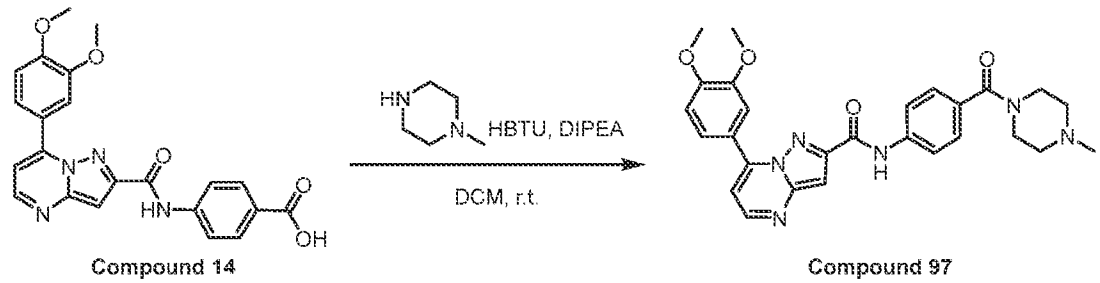
Synthesis of Compound 14



Compound 11 Compound 14

[00445] Compound 11 (550 mg, 1.22 mmol) was dissolved in H2O/THF/MeOH (5/8/4 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 2.44 mL) and stirred at 60 °C for 30 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the solid was filtered by using H_2O. The reaction mixture was purified by MPLC to give compound 14, 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoic acid (464 mg, 91%) as a yellow solid.

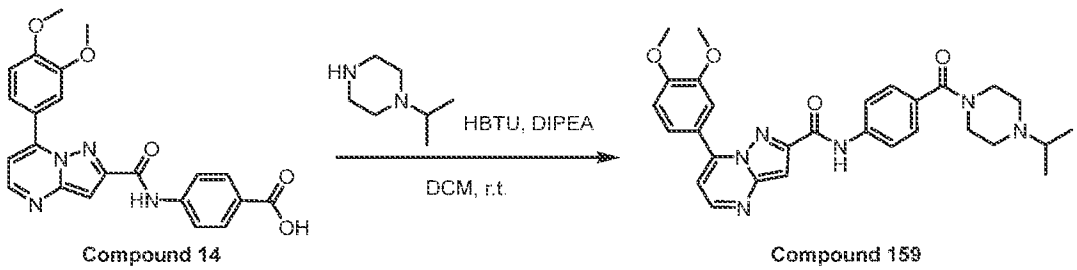
Synthesis of Compound 97



Compound 14 Compound 97

[00446] Compound 14 (80 mg, 0.183 mmol), 1-methylpiperazine (0.022 mL, 0.202 mmol), HBTU (77 mg, 0.202 mmol), diisopropylethylamine (0.063 mL, 0.366 mmol) were combined in DCM. After stirring for 24 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$ and purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 97, 7-(3,4-dimethoxyphenyl)-N-(4-(4-methylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (43.8 mg, 46% yield) as a white solid.

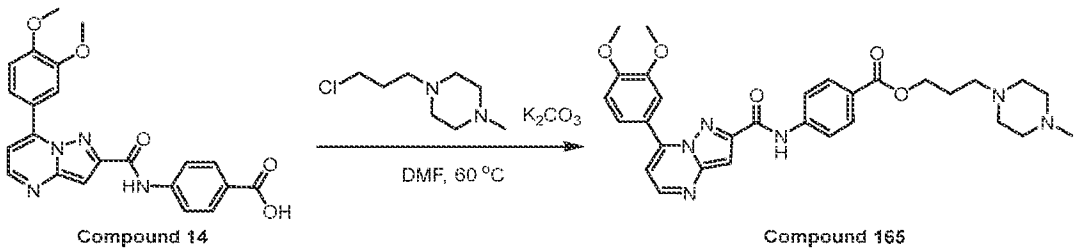
Synthesis of Compound 159



Compound 14 Compound 159

[00447] Compound 14 (1700 mg, 4.063 mmol), 1-isopropylpiperazine (0.637 mL, 4.469 mmol), HBTU (1695 mg, 4.469 mmol), diisopropylethylamine (1.4 mL, 8.126 mmol) were combined in DCM. After stirring for 26 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$ and purified by MPLC. The crude mixture was solidified using DCM and diethyl ether to give compound 159, 7-(3,4-dimethoxyphenyl)-N-(4-(4-isopropylpiperazine-1-carbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (1641.6 mg, 76% yield) as a white solid.

Synthesis of Compound 165

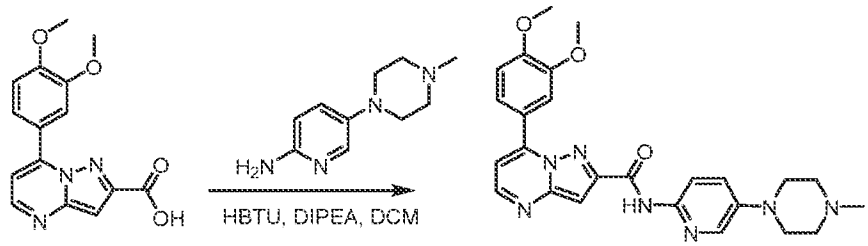


Compound 14 Compound 165

[00448] Compound 14 (180 mg, 0.43 mmol), 1-(3-chloropropyl)-4-methylpiperazine (0.15 mL, 0.86 mmol) and potassium carbonate (178 mg, 1.29 mmol) were combined in DMF and heated to 60 °C for

26 hr. The reaction mixture was extracted by DCM and aq. NH_4Cl and purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 165, 3-(4-methylpiperazin-1-yl)propyl 4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate (15.31 mg, 6% yield) as a white solid.

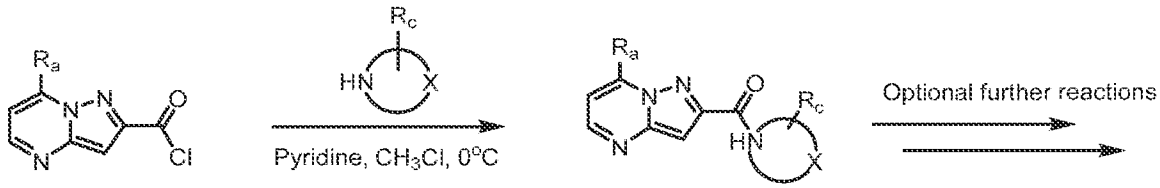
Synthesis of Compound 204



Compound 204

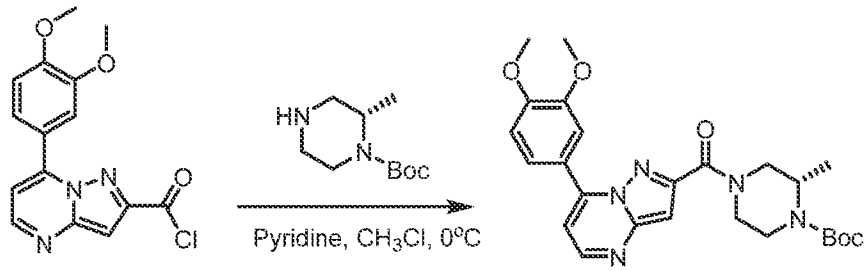
[00449] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (114 mg, 0.38 mmol), 5-(4-methylpiperazin-1-yl)pyridin-2-amine (80 mg, 0.42 mmol), HBTU (159 mg, 0.42 mmol), diisopropylethylamine (0.196 mL, 1.14 mmol) were combined in DCM. After stirring for 22 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 204, 7-(3,4-dimethoxyphenyl)-N-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (120 mg, 67% yield) as a yellow solid.

General Method D



Formula II-b

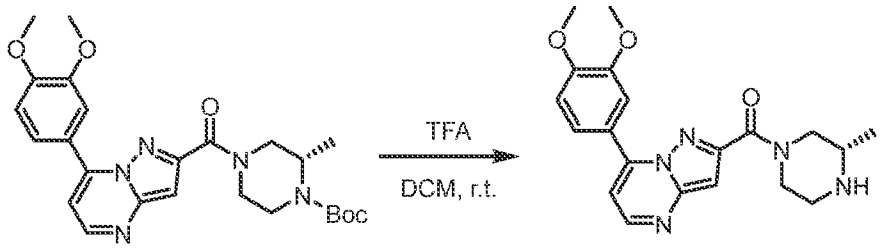
Synthesis of Compound 112



Compound 112

[00450] To a solution of ((S)-1-N-Boc-2-methylpiperazine) (1205 mg, 6.014 mmol) and pyridine (2.724 mL, 33.410mmol) in chloroform (66.82 mL), 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl chloride (2123 mg, 6.682 mmol) dissolved in chloroform (134 mL) was added dropwise and stirred for 4.5 hr at 0 ℃. The reaction mixture was extracted by EA and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was solidified using DCM, hexane and diethyl ether to give compound 112, tert-butyl (S)-4-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2-methylpiperazine-1-carboxylate . (2335.6 mg, 73%) as a beige solid.

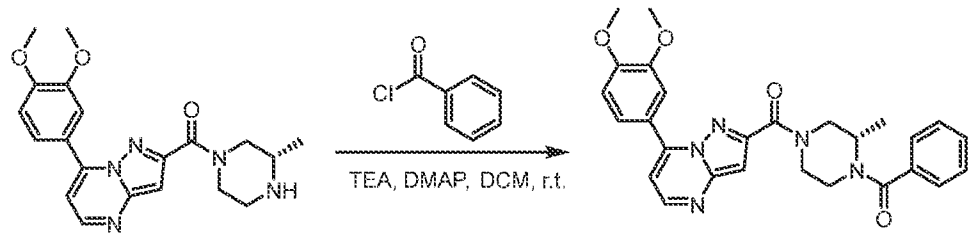
Synthesis of Compound 181



Compound 112 Compound 181

[00451] Compound 112 (2335 mg, 4.849 mmol), TFA (3.614 ml, 48.489 mmol) were combined in DCM (48.489 mL) at r.t. for 20 hr. After evaporation, the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give compound 181, (S)-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(3-methylpiperazin-1-yl)methanone (1784 mg, 97%) as a yellow solid.

Synthesis of Compound 210

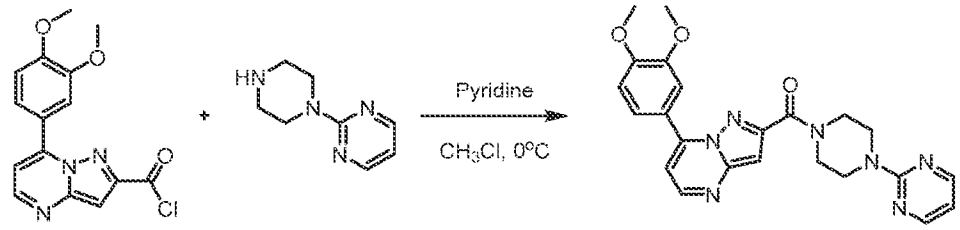


Compound 181 Compound 210

[00452] Compound 181 (1784 mg, 4.688 mmol), benzoyl chloride (986 mg, 7.016 mmol), TEA (2366 mg, 23.385 mmol), DMAP (6 mg, 0.01 eq) were combined in DCM at r.t. for 14 hr. The reaction mixture was extracted by DCM and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and isopropyl ether to give compound 210, (S)-(4-benzoyl-3-

methylpiperazin-1-yl)(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)methanone (1689 mg, 74% yield) as a yellow solid.

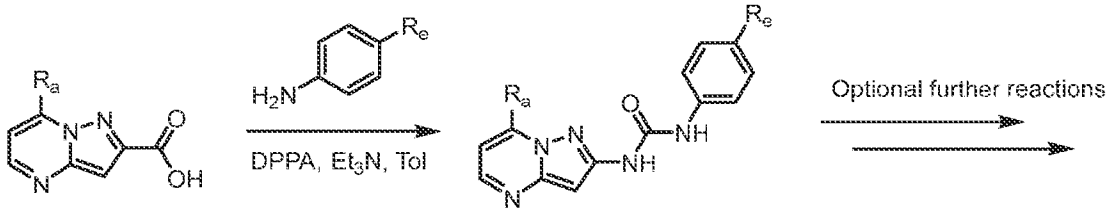
Synthesis of Compound 185



Compound 185

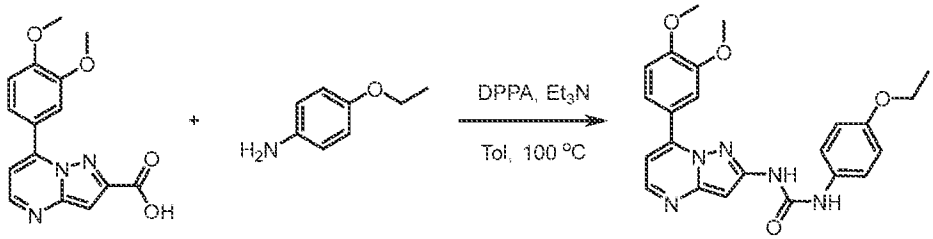
[00453] To a solution of 2-(piperazin-1-yl)pyrimidine (36 mg, 0.22 mmol) and pyridine (0.036 mL, 0.44 mmol) in chloroform (2 mL), 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carbonyl chloride (70 mg, 0.22 mmol) dissolved in chloroform (2 mL) was added dropwise and stirred for 2 hr at 0 °C. The reaction mixture was extracted by EA and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was solidified using DCM, hexane and diethyl ether to give compound 185, (7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (50 mg, 51%) as a white solid.

General Method E



Formula II-a

Synthesis of Compound 109

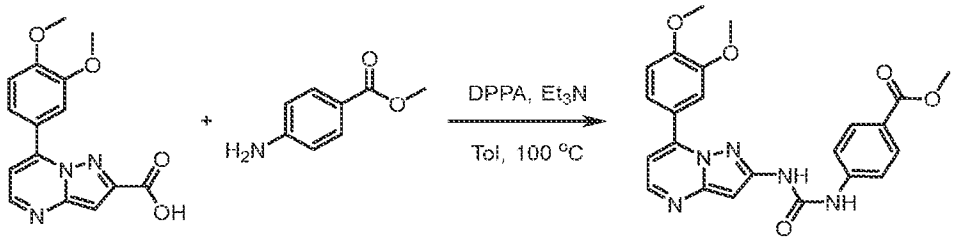


Compound 109

[00454] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (80 mg, 0.267 mmol), p-phenetidine (0.023 mL, 0.178 mmol), DPPA (0.046 mL, 0.214 mmol), TEA (0.075 mL,

0.534 mmol) were combined in toluene (1 mL). The mixture was stirred in microwave at 100 °C for 25 min. The reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 109, 1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-(4-ethoxyphenyl)urea (25 mg, 22% yield) as a pale grey solid.

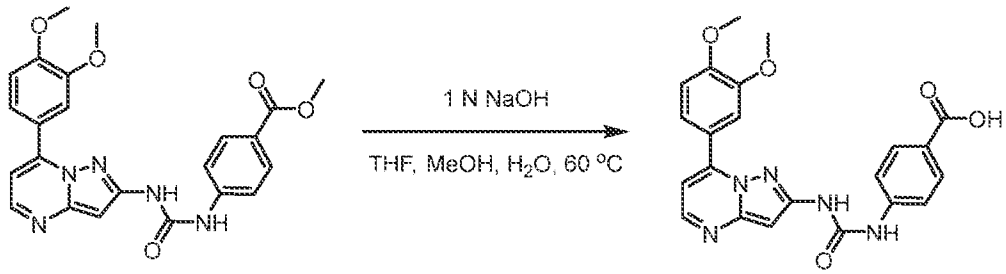
Synthesis of Compound 93



Compound 93

[00455] 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (80 mg, 0.267 mmol), methyl 4-aminobenzoate (30.3 mg, 0.200 mmol), DPPA (0.047 mL, 0.216 mmol), TEA (0.083 mL, 0.594 mmol) were combined in toluene (1 mL). The mixture was stirred in microwave at 100 °C for 15 min. The reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM, methanol and hexane to give compound 93, methyl 4-(3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)ureido)benzoate (55.5 mg, 42% yield) as a pale yellow solid.

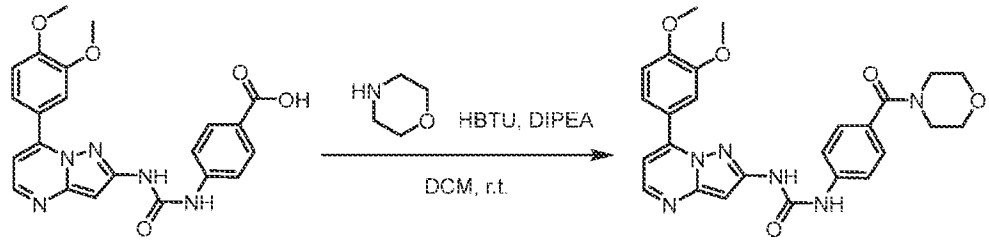
Synthesis of Compound 107



Compound 93 Compound 107

[00456] Compound 93 (55 mg, 0.123 mmol) was dissolved in H_2O/THF/MeOH (0.5/0.8/0.4 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 0.246 mL) and stirred at 60 °C for 7 hr. After cooling at 0 °C, the mixture was acidified by adding 1 N HCl. Then the solid was filtered by using H_2O to give compound 107, 4-(3-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)ureido)benzoic acid (31.4 mg, 59% yield) as an orange solid.

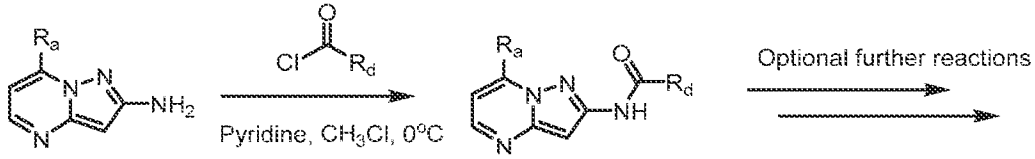
Synthesis of Compound 129



Compound 107 Compound 129

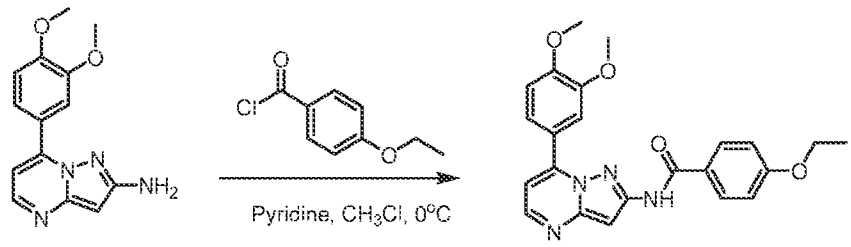
[00457] Compound 107 (24 mg, 0.0554 mmol), morpholine (0.005 mL, 0.0609 mmol), HBTU (23 mg, 0.0609 mmol), diisopropylethylamine (0.019 mL, 0.1108 mmol) were combined in DCM. After stirring for 22 hr at r.t., the reaction mixture was extracted by DCM and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 129, 1-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)-3-(4-(morpholine-4-carbonyl)phenyl)urea (16 mg, 57% yield) as a pale yellow solid.

General Method F



Formula II-d

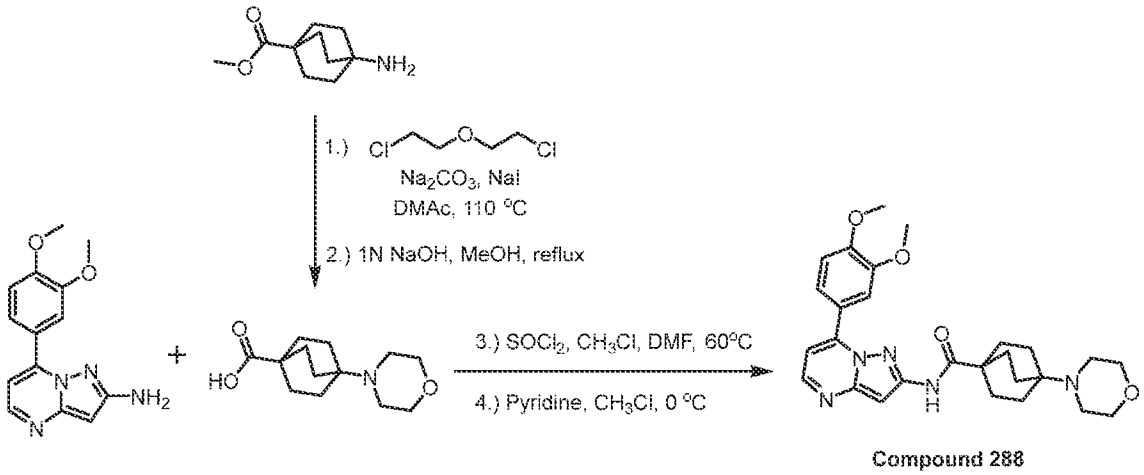
Synthesis of Compound 287



Formula II-d Compound 287

[00458] To a solution of 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-amine (31 mg, 0.12 mmol) and pyridine (0.019 mL, 0.23 mmol) in chloroform (1 mL), 4-ethoxybenzoyl chloride (21 mg, 0.12 mmol) dissolved in chloroform (1 mL) was added dropwise and stirred for 2 hr at 0 °C. The reaction mixture was extracted by EA and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The reaction mixture was purified by MPLC to give compound 287, *N*-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)-4-ethoxybenzamide as a white solid. (20 mg, 42%)

Synthesis of Compound 288



Step 1

[00459] Methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate (109 mg, 0.59 mmol), 2-chloro ethyl ether (0.077 mL, 0.65 mmol), sodium carbonate (189 mg, 1.78 mmol) and sodium iodide (178 mg, 1.19 mmol) were combined in N,N-dimethylacetamide (DMAc) (2 mL) and stirred at 110 °C. 2-Chloro ethyl ether (0.070 mL) was added twice for every 30 minutes. After 16 hr, the mixture was extracted by DCM and H_2O. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give methyl 4-morpholinobicyclo[2.2.2]octane-1-carboxylate (115.5 mg, 77%) as a white solid.

Step 2

[00460] Methyl 4-morpholinobicyclo[2.2.2]octane-1-carboxylate (143 mg, 0.56 mmol) was dissolved in MeOH (5 mL), followed up by addition of sodium hydroxide in H_2O (1 N, 1.130 mL) and heated to reflux for 2 hr. The mixture was concentrated to give 4-morpholinobicyclo[2.2.2]octane-1-carboxylic acid (51 mg, 38%) as a pale red solid.

Step 3

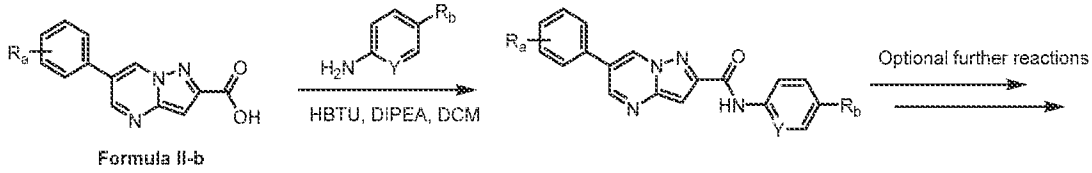
[00461] To a solution of 4-morpholinobicyclo[2.2.2]octane-1-carboxylic acid (32 mg, 0.13 mmol) in Chloroform (2 mL), DMF (catalytic amount) and $SOCl_2$ (0.048 mL, 0.67 mmol) were added and stirred at 60 °C for 2 hr. The mixture was concentrated to give 4-morpholinobicyclo[2.2.2]octane-1-carbonyl chloride (34 mg, 99%).

Step 4

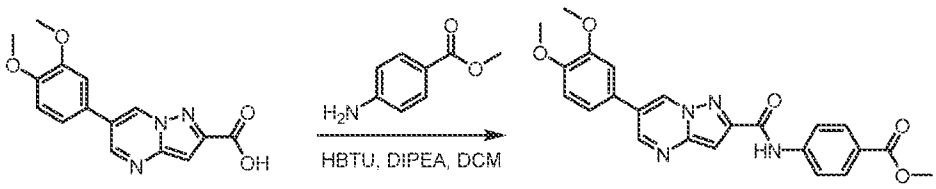
[00462] To a solution of 2-(piperazin-1-yl)pyrimidine (36 mg, 0.13 mmol) and pyridine (0.054 mL, 0.67 mmol) in chloroform (2 mL), 4-morpholinobicyclo[2.2.2]octane-1-carbonyl chloride (34 mg, 0.13 mmol) dissolved in chloroform (2 mL) was added dropwise and stirred for 2 hr at 0 °C. The

reaction mixture was extracted by EA and aq. $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was purified by MPLC to give compound 288, N-(7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidin-2-yl)-4-morpholinobicyclo[2.2.2]octane-1-carboxamide (24.1 mg, 37%) as a pale yellow solid.

General Method G



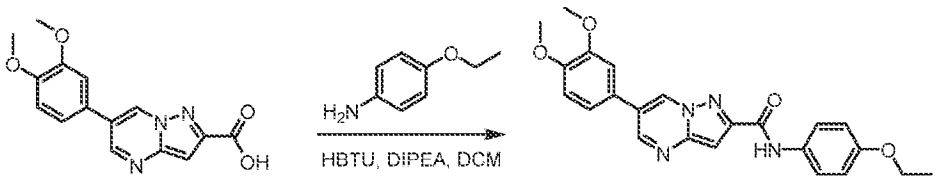
Synthesis of Compound 239



Compound 239

[00463] 6-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (50 mg, 0.0554 mmol), methyl 4-aminobenzoate (28 mg, 0.184 mmol), HBTU (70 mg, 0.184 mmol), diisopropylethylamine (0.058 mL, 0.334 mmol) were combined in DCM. After stirring for 22 hr at r.t., the reaction mixture was extracted by EA and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 239, methyl 4-(6-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamido)benzoate (12 mg, 17% yield) as a white solid.

Synthesis of Compound 254

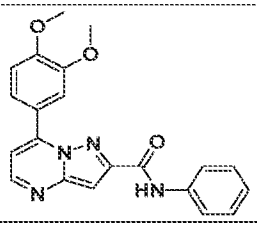
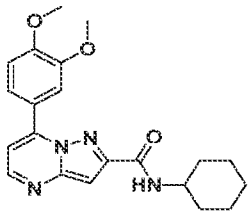
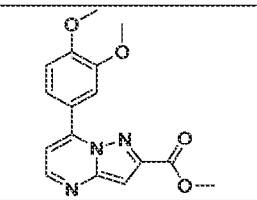
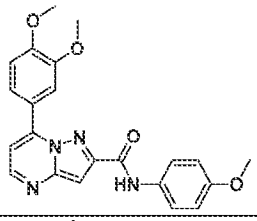
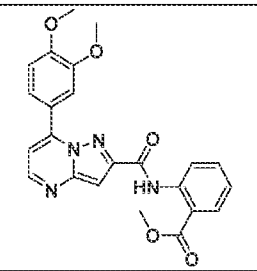
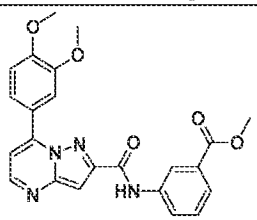


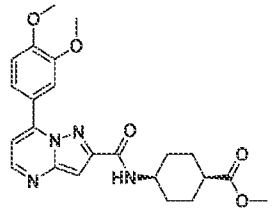
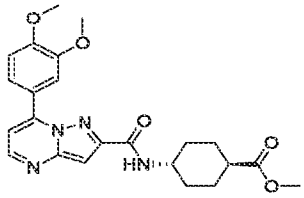
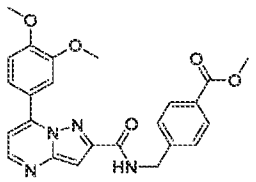
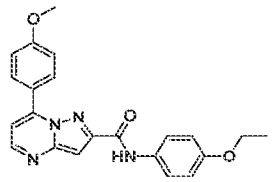
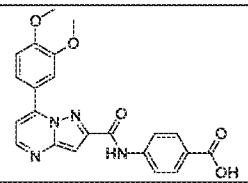
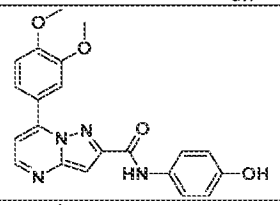
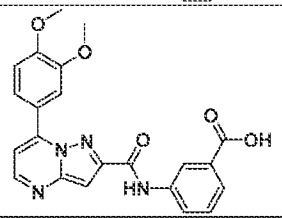
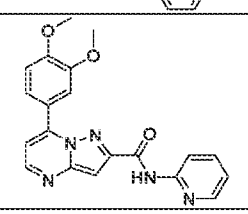
Compound 254

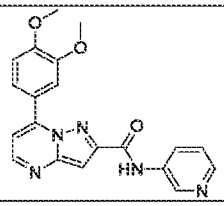
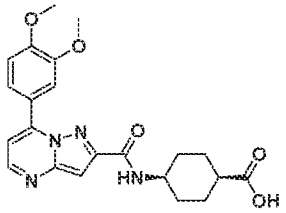
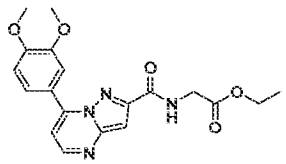
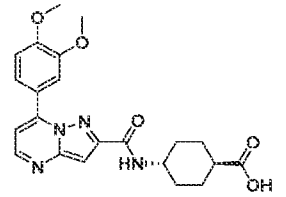
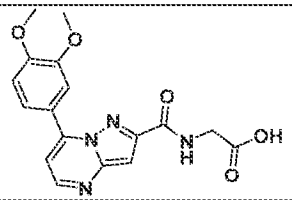
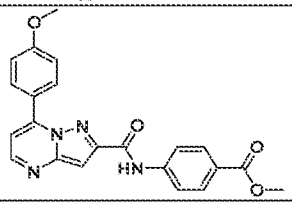
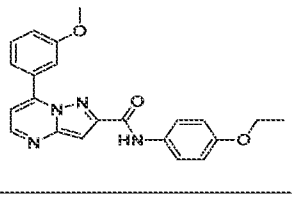
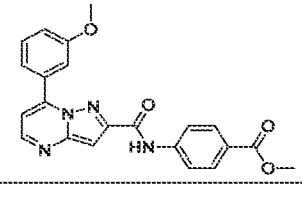
[00464] 6-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (34.4 mg, 0.115 mmol), p-phenetidine (0.016 mL, 0.126 mmol), HBTU (48 mg, 0.126 mmol), diisopropylethylamine (0.040 mL, 0.230 mmol) were combined in DCM. After stirring for 22 hr at r.t., the reaction mixture was extracted by EA and aq. $NaHCO_3$. The reaction mixture was purified by MPLC. The crude mixture was solidified using DCM and hexane to give compound 254, 6-(3,4-dimethoxyphenyl)-N-(4-ethoxyphenyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide (10 mg, 21% yield) as a white solid.

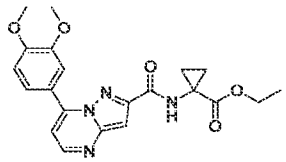
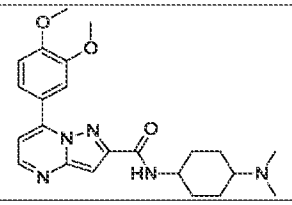
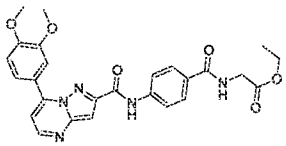
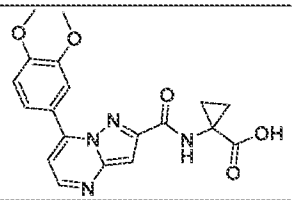
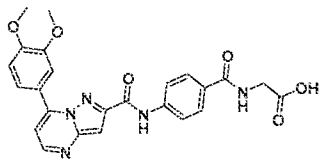
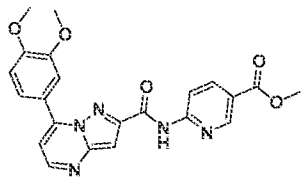
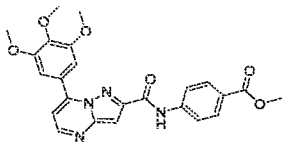
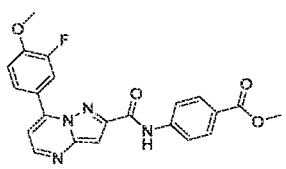
[00465] The chemical structures, selected characterizations, and synthetic methods of the compound of the present disclosure are tabulated in Tables 3A and 3B below.

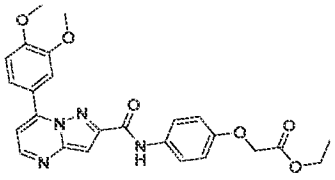
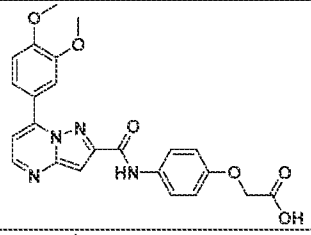
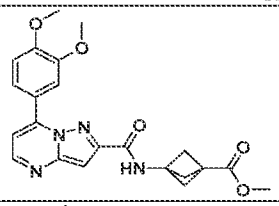
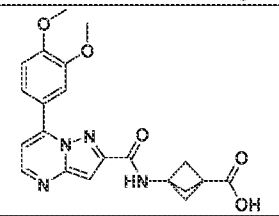
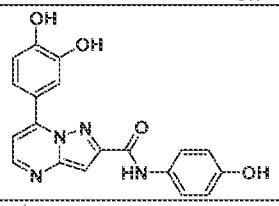
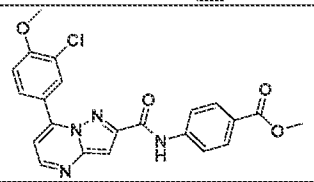
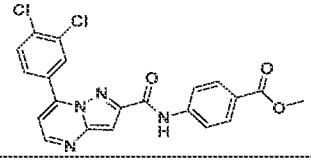
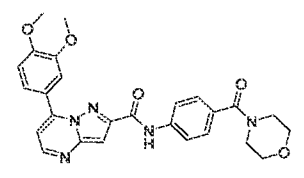
Table 3A – Compound Structures, Characterization Data and Synthetic Method

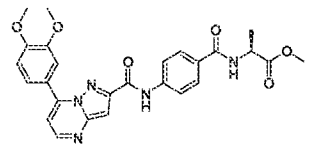
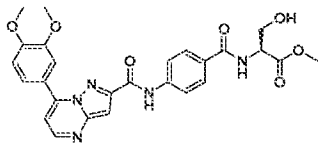
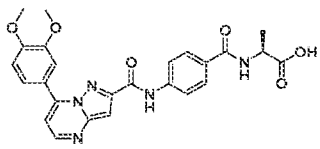
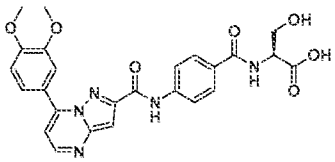
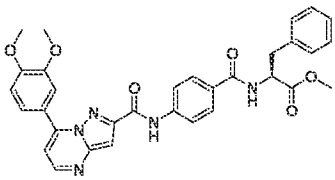
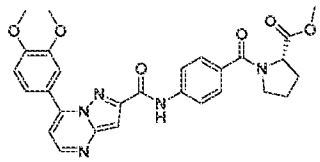
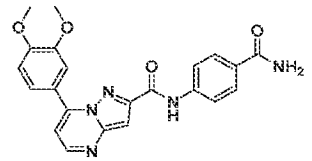
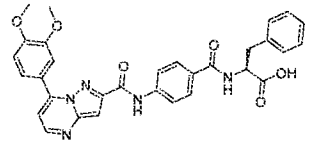
Cmpd	Structure	Characterization Data	General Method (Ex. 2)
1		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.0 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.38 (t, J = 7.9 Hz, 2H), 7.30 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 3.93 – 3.87 (m, 6H).	C
2		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.90 – 3.88 (m, 6H), 3.85 – 3.76 (m, 1H), 1.90 – 1.68 (m, 4H), 1.66 – 1.55 (m, 1H), 1.45 – 1.24 (m, 4H), 1.21 – 1.07 (m, 1H).	A
4		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 4.4 Hz, 1H), 7.87 (dd = 8.6, 2.4 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.25 (s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H).	A (Example 1)
6		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.27 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 9.1 Hz, 2H), 3.92 – 3.89 (m, 6H), 3.76 (s, 3H).	C
7		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H), 8.87 (d, J = 8.5 Hz, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.25 (dd, J = 8.5, 2.0 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 1.9 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 4.5 Hz, 1H), 7.31 (s, 1H), 7.29 – 7.21 (m, 2H), 3.95 (s, 3H), 3.92 – 3.89 (m, 6H).	C
8		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.52 (s, 1H), 8.13 – 8.06 (m, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.93 – 3.87 (m, 9H).	C

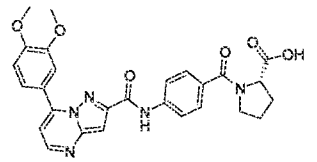
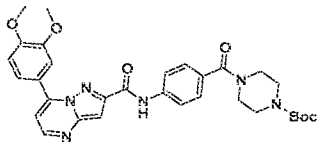
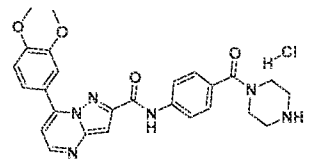
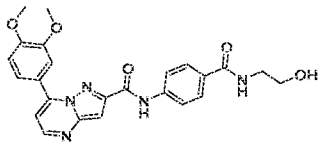
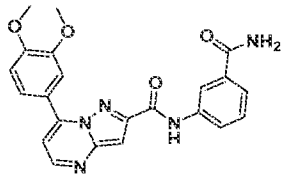
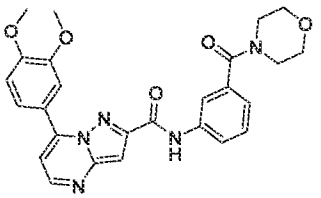
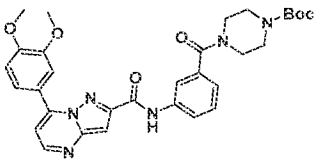
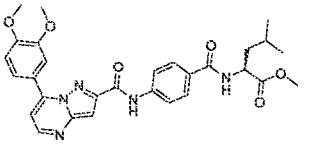
9		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.14 (s, 1H), 3.99 – 3.86 (m, 7H), 3.64 (s, 3H), 2.65 – 2.57 (m, 1H), 2.01 – 1.88 (m, 2H), 1.74 – 1.56 (m, 6H).	A
10		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 8.5, 2.1 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.91 – 3.88 (m, 6H), 3.86 – 3.74 (m, 1H), 3.61 (s, 3H), 2.35 – 2.24 (m, 1H), 2.01 – 1.83 (m, 4H), 1.52 – 1.35 (m, 4H).	A
12		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (t, J = 6.3 Hz, 1H), 8.66 (dd, J = 4.5, 0.7 Hz, 1H), 7.97 – 7.90 (m, 3H), 7.86 (d, J = 1.4 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.44 – 7.41 (m, 1H), 7.21 – 7.15 (m, 2H), 4.60 (d, J = 6.2 Hz, 2H), 3.90 – 3.83 (m, 9H).	A
13		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.35 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 4.5 Hz, 1H), 7.26 (s, 1H), 7.20 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.1 Hz, 2H), 4.03 (q, J = 7.0 Hz, 2H), 3.90 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H).	C
14		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 10.53 (s, 1H), 8.71 (d, J = 4.1 Hz, 1H), 8.09 – 7.84 (m, 6H), 7.50 (d, J = 4.3 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 4.00 – 3.82 (m, 6H).	C
15		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.32 (s, 1H), 8.68 (d, J = 3.4 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 4.3 Hz, 1H), 7.28 – 7.15 (m, 2H), 6.77 (d, J = 7.7 Hz, 2H), 3.94 – 3.88 (m, 6H).	C
16		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.47 – 8.44 (m, 1H), 8.10 – 8.00 (m, 2H), 7.95 (d, J = 2.1 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.92 – 3.89 (m, 6H).	C
17		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.76 – 8.67 (m, 1H), 8.45 – 8.37 (m, 1H), 8.25 (d, J = 8.3 Hz, 1H), 7.99 – 7.87 (m, 3H), 7.53 – 7.48 (m, 1H), 7.39 (d, J = 3.5 Hz, 1H), 7.30 – 7.17 (m, 2H), 3.96 – 3.89 (m, 6H).	C

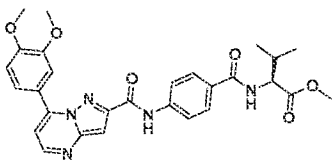
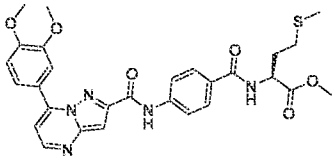
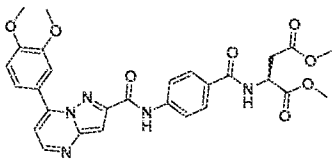
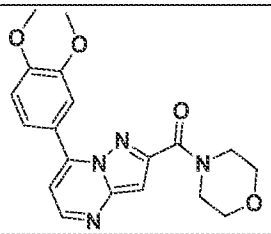
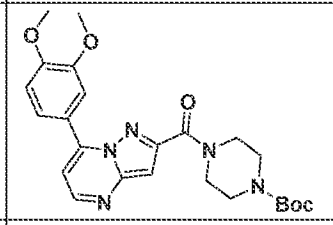
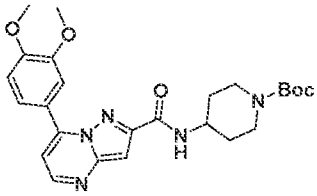
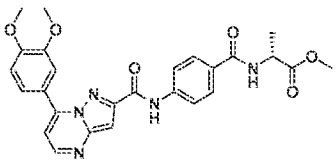
18		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.98 (d, J = 2.1 Hz, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.40 – 8.33 (m, 1H), 8.29 – 8.20 (m, 1H), 8.09 – 7.90 (m, 2H), 7.58 – 7.39 (m, 2H), 7.33 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 4.01 – 3.88 (m, 6H).	C
19		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.94 – 7.88 (m, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.21 (s, 1H), 7.14 (s, 1H), 3.94 – 3.86 (m, J = 8.0 Hz, 7H), 2.48 – 2.43 (m, 1H), 1.99 – 1.90 (m, 2H), 1.72 – 1.57 (m, 6H).	A
20		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (t, J = 6.0 Hz, 1H), 8.67 (d, J = 4.5 Hz, 1H), 7.93 (dd, J = 8.5, 2.1 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.16 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.06 (d, J = 6.1 Hz, 2H), 3.91 – 3.87 (m, 6H), 1.21 (t, J = 7.1 Hz, 3H).	A
21		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.64 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.92 – 3.87 (m, 6H), 3.82 – 3.73 (m, 1H), 2.22 – 2.12 (m, 1H), 2.02 – 1.85 (m, 4H), 1.52 – 1.35 (m, 4H).	A
22		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.5 Hz, 1H), 8.60 (t, J = 5.4 Hz, 1H), 7.92 (dd, J = 8.5, 2.1 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 0.6 Hz, 1H), 3.98 (d, J = 6.0 Hz, 2H), 3.92 – 3.86 (m, 6H).	A
23		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.35 (d, J = 8.8 Hz, 2H), 8.00 (s, 4H), 7.43 (d, J = 4.4 Hz, 1H), 7.34 (s, 1H), 7.20 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 3.85 (s, 3H).	C
24		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.72 (d, J = 4.2 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.56 (t, J = 7.9 Hz, 1H), 7.45 (d, J = 4.3 Hz, 1H), 7.31 (s, 1H), 7.24 (d, J = 7.7 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 4.02 (q, J = 13.9, 6.9 Hz, 2H), 3.88 (s, 3H), 1.33 (t, J = 6.9 Hz, 3H).	C
25		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 8.74 (d, J = 4.4 Hz, 1H), 7.98 (s, 4H), 7.86 – 7.79 (m, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.38 (s, 1H), 7.24 (dd, J = 8.3, 2.5 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H).	C

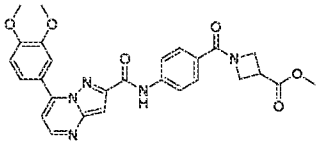
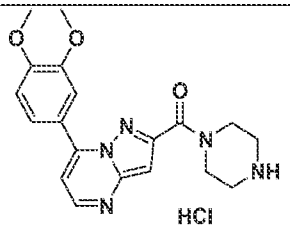
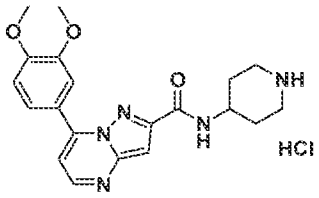
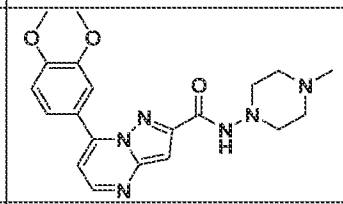
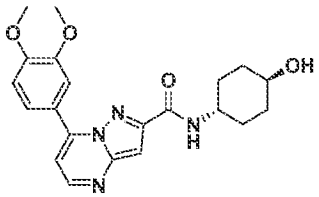
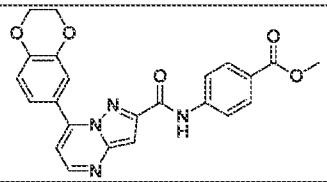
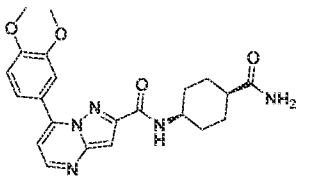
26		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.66 (d, J = 4.5 Hz, 1H), 7.99 (dd, J = 8.5, 2.0 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 4.4 Hz, 1H), 7.23 – 7.12 (m, 2H), 4.10 – 4.03 (m, 2H), 3.93 – 3.87 (m, 6H), 1.51 – 1.46 (m, 2H), 1.25 – 1.20 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H).	A
27		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.00 - 7.92 (m, 3H), 7.42 (d, J = 4.5 Hz, 1H), 7.22 - 7.14 (m, 2H), 4.04 - 3.94 (m, 1H), 3.93 - 3.85 (m, 6H), 2.30 - 2.08 (m, 7H), 1.86 - 1.68 (m, 4H), 1.65 - 1.48 (m, 4H).	A
28		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.89 (t, J = 5.8 Hz, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.97 – 7.88 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.00 (d, J = 5.8 Hz, 2H), 3.95 – 3.87 (m, 6H), 1.22 (t, J = 7.1 Hz, 3H).	C
29		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.99 (dd, J = 8.5, 2.2 Hz, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.14 (s, 1H), 3.91 – 3.87 (m, 6H), 1.47 – 1.39 (m, 2H), 1.22 – 1.15 (m, 2H).	A
30		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 10.50 (s, 1H), 8.79 (t, J = 5.9 Hz, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.98 – 7.87 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.96 – 3.87 (m, 8H).	C
31		^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.97 (d, J = 2.1 Hz, 1H), 8.63 (d, J = 4.3 Hz, 1H), 8.52 (d, J = 8.7 Hz, 1H), 8.39 (dd, J = 8.7, 2.2 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.71 (dd, J = 8.4, 2.1 Hz, 1H), 7.45 (s, 1H), 7.21 – 7.07 (m, 2H), 4.13 – 4.03 (m, 6H), 3.97 (s, 3H).	B
32		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.74 (d, J = 4.4 Hz, 1H), 8.04 – 7.92 (m, 4H), 7.67 (s, 2H), 7.57 (d, J = 4.4 Hz, 1H), 7.37 (s, 1H), 3.96 – 3.88 (m, 6H), 3.85 (s, 3H), 3.80 (s, 3H).	C
33		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.33 (dd, J = 12.8, 2.2 Hz, 1H), 8.24 (d, J = 8.7 Hz, 1H), 8.00 (s, 4H), 7.51 (d, J = 4.5 Hz, 1H), 7.44 (t, J = 8.9 Hz, 1H), 7.37 (s, 1H), 3.99 (s, 3H), 3.85 (s, 3H).	C

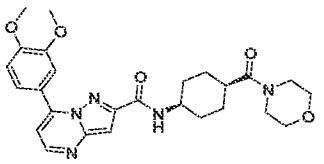
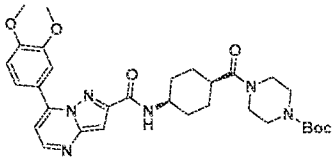
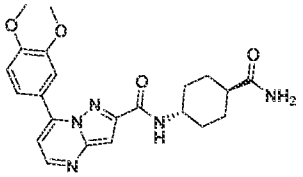
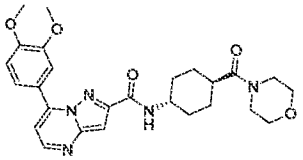
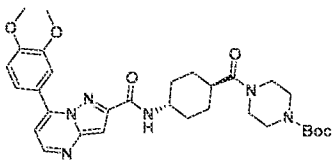
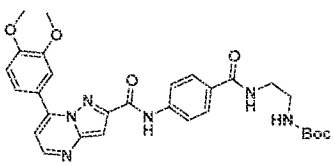
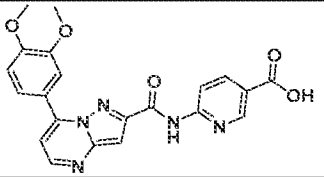
34		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.71 (d, J = 9.1 Hz, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 9.1 Hz, 2H), 4.77 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.96 – 3.87 (m, 6H), 1.22 (t, J = 7.1 Hz, 3H).	C
35		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 10.16 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 1.9 Hz, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 4.66 (s, 2H), 3.93 – 3.87 (m, 6H).	C
36		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.64 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.12 (s, 1H), 3.91 – 3.86 (m, 6H), 3.63 (s, 3H), 2.36 (s, 6H).	B
37		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H), 9.03 (s, 1H), 8.64 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.12 (s, 1H), 3.93 – 3.87 (m, 6H), 2.32 (s, 6H).	B
38		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.74 - 9.06 (m, 3H), 8.61 (d, J = 4.5 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 7.69 (dd, J = 8.4, 2.3 Hz, 1H), 7.56 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 4.5 Hz, 1H), 7.21 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.9 Hz, 2H).	C
39		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.50 – 8.33 (m, 2H), 8.09 – 7.90 (m, 4H), 7.50 (d, J = 4.4 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.37 (s, 1H), 4.01 (s, 3H), 3.85 (s, 3H).	C
40		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.77 (d, J = 4.4 Hz, 1H), 8.52 (d, J = 2.1 Hz, 1H), 8.31 (dd, J = 8.5, 2.1 Hz, 1H), 7.99 (s, 4H), 7.93 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 4.4 Hz, 1H), 7.41 (s, 1H), 3.85 (s, 3H).	C
41		^{1}H NMR (400 MHz, DMSO-$d6$) δ 10.43 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.01 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.32 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.93 – 3.87 (m, 6H), 3.67 – 3.39 (m, 8H).	C

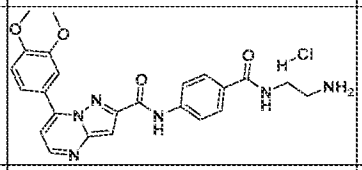
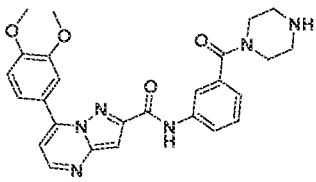
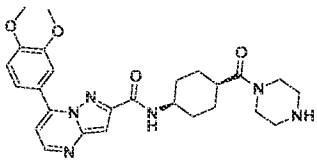
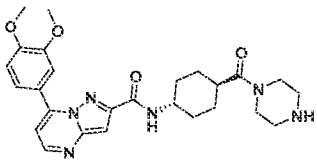
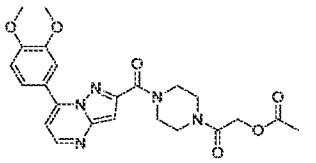
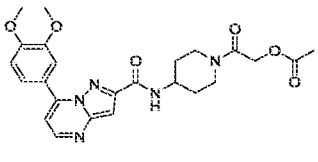
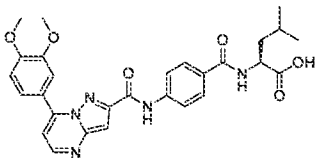
42		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.77 – 8.64 (m, 2H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.99 – 7.84 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.57 – 4.41 (m, 1H), 3.95 – 3.83 (m, 6H), 3.66 (s, 3H), 1.42 (d, J = 7.3 Hz, 3H).	C
43		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.51 (d, J = 7.3 Hz, 1H), 8.09 – 7.99 (m, 1H), 7.99 – 7.88 (m, 5H), 7.51 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 5.07 (t, J = 6.1 Hz, 1H), 4.64 – 4.40 (m, 1H), 3.98 – 3.87 (m, 6H), 3.81 (t, J = 5.7 Hz, 2H), 3.67 (s, 3H).	C
44		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.47 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.58 (d, J = 7.2 Hz, 1H), 8.09 – 8.00 (m, 1H), 8.00 – 7.84 (m, 5H), 7.50 (d, J = 4.4 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.54 – 4.29 (m, 1H), 4.00 – 3.71 (m, 6H), 1.41 (d, J = 7.3 Hz, 3H).	C
45		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 10.47 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.32 (d, J = 7.7 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.99 – 7.85 (m, 5H), 7.49 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.98 (s, 1H), 4.56 – 4.36 (m, 1H), 3.98 – 3.85 (m, 6H), 3.85 – 3.67 (m, 2H).	C
46		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.79 (d, J = 7.6 Hz, 1H), 8.71 (d, J = 4.2 Hz, 1H), 8.08 – 7.77 (m, 6H), 7.50 (d, J = 4.3 Hz, 1H), 7.40 – 7.14 (m, 7H), 4.73 – 4.57 (m, 1H), 4.02 – 3.80 (m, 6H), 3.65 (s, 3H), 3.24 – 3.03 (m, 2H).	C
47		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 – 10.31 (m, 1H), 8.71 (d, J = 4.3 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.99 – 7.81 (m, 3H), 7.68 – 7.36 (m, 3H), 7.33 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 4.57 – 4.42 (m, 1H), 3.99 – 3.81 (m, 6H), 3.74 – 3.41 (m, 5H), 2.37 – 2.21 (m, 1H), 2.03 – 1.73 (m, 3H).	C
48		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.94 – 7.87 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.22 (d, J = 8.6 Hz, 1H), 3.94 – 3.87 (m, 6H).	C
49		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 10.46 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.12 – 7.72 (m, 6H), 7.50 (d, J = 4.4 Hz, 1H), 7.39 – 7.07 (m, 7H), 4.62 (s, 1H), 4.06 – 3.66 (m, 6H), 3.24 – 3.04 (m, 2H).	C

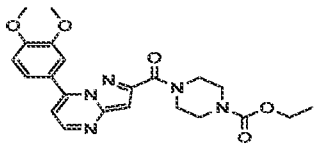
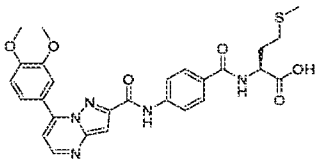
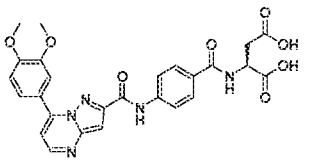
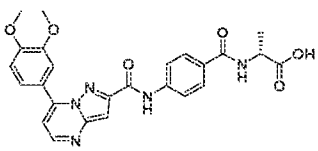
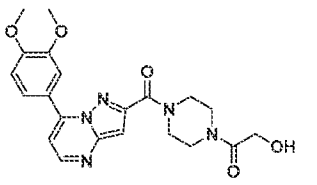
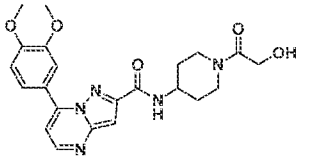
50		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.56 – 10.40 (m, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.97 – 7.78 (m, 3H), 7.65 – 7.37 (m, 3H), 7.33 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 4.48 – 4.35 (m, 1H), 4.05 – 3.76 (m, 6H), 3.68 – 3.45 (m, 2H), 2.38 – 2.10 (m, 1H), 2.05 – 1.66 (m, 3H).	C
51		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.45 (d, J = 8.6 Hz, 2H), 7.32 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.92 – 3.88 (m, 6H), 3.61 – 3.35 (m, 8H), 1.41 (s, 9H).	C
52		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.46 (s, 2H), 8.70 (d, J = 4.5 Hz, 1H), 8.01 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.53 – 7.48 (m, 3H), 7.35 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.92 – 3.86 (m, 6H), 3.81 – 3.64 (m, 4H), 3.21 – 3.09 (m, 4H).	C
53		^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.63 (d, J = 4.4 Hz, 1H), 7.89 – 7.75 (m, 5H), 7.75 – 7.67 (m, 2H), 7.41 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 4.4 Hz, 1H), 6.70 (s, 1H), 4.11 – 4.00 (m, 6H), 3.92 – 3.85 (m, 2H), 3.71 – 3.65 (m, 2H).	C
54		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.61 (d, J = 4.4 Hz, 1H), 8.18 (s, 1H), 8.00 – 7.92 (m, 1H), 7.91 – 7.80 (m, 3H), 7.54 (d, J = 7.7 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.29 (s, 1H), 7.23 (s, 1H), 7.13 (d, J = 8.5 Hz, 1H), 3.83 – 3.78 (m, 6H).	C
55		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.52 – 7.43 (m, 2H), 7.32 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.19 – 7.16 (m, 1H), 3.94 – 3.87 (m, 6H), 3.74 – 3.35 (m, 8H).	C
56		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.63 (s, 1H), 7.85 (s, 1H), 7.73 (dd, J = 8.4, 2.1 Hz, 2H), 7.62 (d, J = 2.0 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 4.0 Hz, 1H), 4.06 (s, 3H), 4.01 (s, 3H), 3.87 – 3.39 (m, 8H), 1.49 (s, 9H).	C
57		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.65 (d, J = 7.7 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.99 – 7.84 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.59 – 4.40 (m, 1H), 3.97 – 3.77 (m, 6H), 3.66 (s, 3H), 1.86 – 1.66 (m, 2H), 1.63 – 1.54 (m, 1H),	C

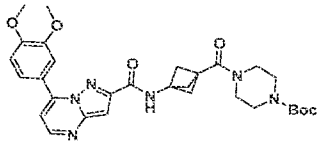
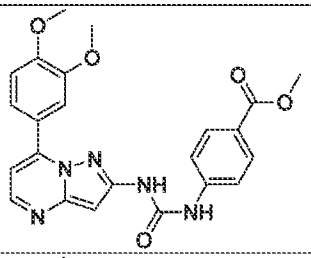
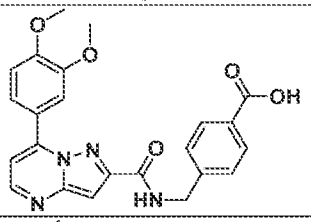
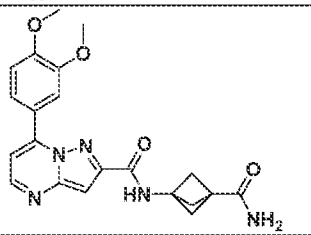
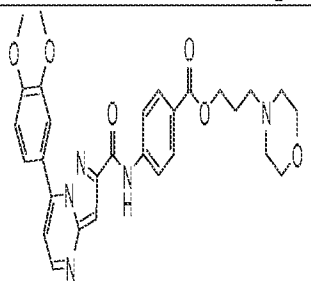
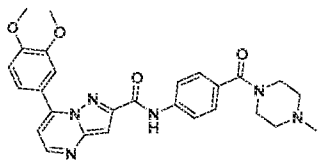
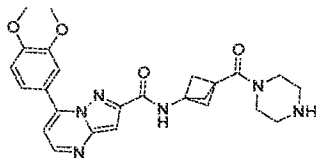
		0.94 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H).	
58		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.52 (d, J = 7.8 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 8.00 – 7.84 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.30 (t, J = 7.6 Hz, 1H), 3.97 – 3.82 (m, 6H), 3.67 (s, 3H), 2.27 – 2.10 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H).	C
59		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.78 – 8.62 (m, 2H), 8.10 – 7.81 (m, 6H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 4.59 (dd, J = 14.3, 7.2 Hz, 1H), 3.97 – 3.83 (m, 6H), 3.67 (s, 3H), 2.70 – 2.53 (m, 2H), 2.12 – 2.03 (m, 5H).	C
60		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.85 (d, J = 7.9 Hz, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.07 – 7.99 (m, 1H), 7.99 – 7.91 (m, 3H), 7.91 – 7.83 (m, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 4.91 – 4.77 (m, 1H), 3.96 – 3.86 (m, 6H), 3.66 (s, 3H), 3.63 (s, 3H), 3.03 – 2.91 (m, 1H), 2.91 – 2.76 (m, 1H).	C
61		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 4.5 Hz, 1H), 7.82 (dd, J = 8.5, 2.1 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 4.5 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.04 (s, 1H), 3.94 – 3.78 (m, 8H), 3.73 – 3.64 (m, 4H), 3.63 – 3.51 (m, 2H).	D
62		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 4.4 Hz, 1H), 7.83 (dd, J = 8.5, 2.0 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 4.5 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.04 (s, 1H), 3.93 – 3.78 (m, 8H), 3.73 – 3.61 (m, 2H), 3.50 – 3.41 (m, 2H), 3.39 – 3.34 (m, 2H), 1.42 (s, 9H).	D
63		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.23 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 8.5, 2.2 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.14 (s, 1H), 4.09 – 3.83 (m, 9H), 2.99 – 2.74 (m, 2H), 1.85 – 1.72 (m, 2H), 1.61 – 1.32 (m, 11H).	A
64		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.84 – 8.56 (m, 2H), 8.19 – 7.73 (m, 6H), 7.68 – 7.43 (m, 1H), 7.34 (s, 1H), 7.23 (d, J = 7.4 Hz, 1H), 4.61 – 4.35 (m, 1H), 4.13 – 3.78 (m, 6H), 3.66 (s, 3H), 1.42 (d, J = 6.6 Hz, 3H).	C

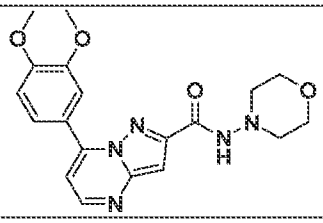
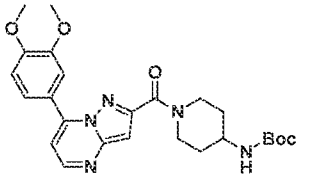
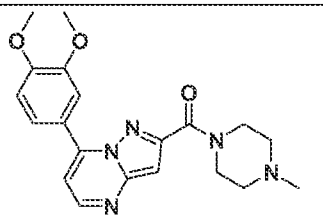
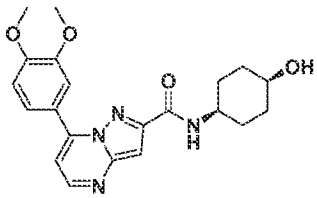
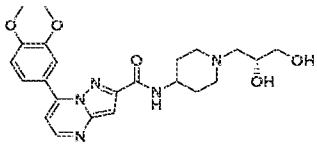
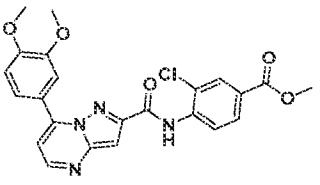
65		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.10 – 8.00 (m, 1H), 8.00 – 7.83 (m, 3H), 7.68 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 4.63 – 4.48 (m, 1H), 4.48 – 4.35 (m, 1H), 4.35 – 4.19 (m, 1H), 4.18 – 4.00 (m, 1H), 3.97 – 3.82 (m, 6H), 3.69 (s, 3H), 3.66 – 3.52 (m, 1H).	C
66		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 2H), 8.68 (d, J = 4.4 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.76 (s, 1H), 7.41 (d, J = 4.4 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.10 (s, 1H), 4.23 – 4.03 (m, 2H), 3.98 – 3.76 (m, 8H), 3.36 – 3.09 (m, 4H).	D
67		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 – 8.83 (m, 1H), 8.81 – 8.68 (m, 1H), 8.66 (d, J = 4.5 Hz, 1H), 8.53 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 8.5, 2.1 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.18 (s, 1H), 4.18 – 4.04 (m, 1H), 3.93 – 3.86 (m, 6H), 3.31 (d, J = 12.2 Hz, 2H), 3.09 – 2.95 (m, 2H), 2.04 – 1.92 (m, 2H), 1.91 – 1.76 (m, 2H).	A
68		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.93 (dd, J = 8.5, 2.2 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.12 (s, 1H), 3.95 – 3.69 (m, 6H), 3.00 – 2.74 (m, 4H), 2.49 – 2.34 (m, 4H), 2.19 (s, 3H).	A
69		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 7.90 (dd, J = 8.4, 2.0 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.12 (s, 1H), 4.57 (d, J = 4.4 Hz, 1H), 3.96 – 3.84 (m, 6H), 3.83 – 3.67 (m, 1H), 3.50 – 3.36 (m, 1H), 1.92 – 1.76 (m, 4H), 1.51 – 1.37 (m, 2H), 1.34 – 1.18 (m, 2H).	A
70		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.03 – 7.92 (m, 4H), 7.91 – 7.82 (m, 2H), 7.41 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.12 (d, J = 8.5 Hz, 1H), 4.46 – 4.14 (m, 4H), 3.86 (s, 3H).	C
71		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.43 (d, J = 4.5 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.15 (s, 1H), 6.75 (s, 1H), 4.06 – 3.95 (m, 1H), 3.94 – 3.85 (m, 6H), 2.31 – 2.21 (m, 1H), 1.87 – 1.70 (m, 4H), 1.70 – 1.48 (m, 4H).	A

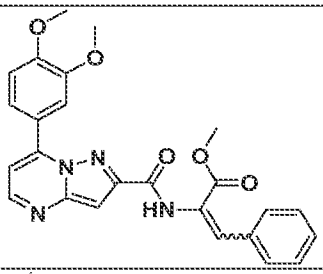
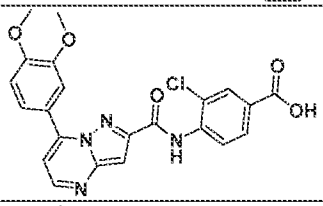
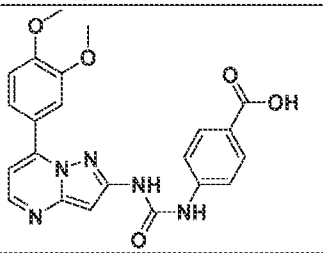
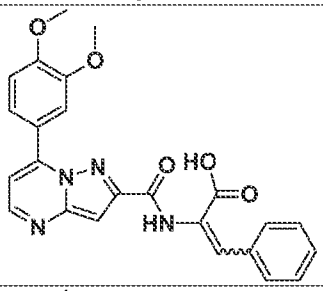
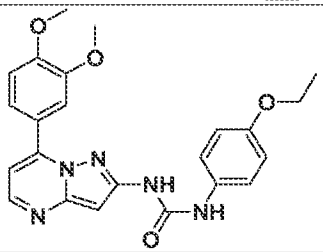
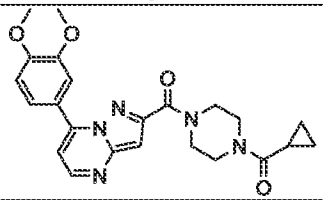
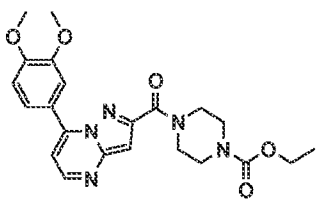
72		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.95 – 7.87 (m, 2H), 7.44 (d, J = 4.5 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.16 (s, 1H), 4.11 – 4.03 (m, 1H), 3.92 – 3.86 (m, 6H), 3.62 – 3.40 (m, 8H), 2.78 – 2.69 (m, 1H), 1.94 – 1.81 (m, 2H), 1.76 – 1.63 (m, 4H), 1.61 – 1.51 (m, 2H).	A
73		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.44 (d, J = 4.5 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.16 (s, 1H), 4.11 – 4.03 (m, 1H), 3.93 – 3.86 (m, 6H), 3.52 – 3.39 (m, 4H), 3.32 – 3.25 (m, 4H), 2.78 – 2.71 (m, 1H), 1.92 – 1.83 (m, 2H), 1.74 – 1.62 (m, 4H), 1.62 – 1.51 (m, 2H), 1.42 (s, 9H).	A
74		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.13 (s, 1H), 6.71 (s, 1H), 3.94 – 3.86 (m, 6H), 3.83 – 3.70 (m, 1H), 2.11 – 2.00 (m, 1H), 1.95 – 1.75 (m, 4H), 1.51 – 1.33 (m, 4H).	A
75		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.2 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.92 – 3.87 (m, 6H), 3.87 – 3.72 (m, 1H), 3.66 – 3.37 (m, 8H), 2.59 – 2.52 (m, 1H), 1.99 – 1.66 (m, 4H), 1.55 – 1.39 (m, 4H).	A
76		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.93 – 3.87 (m, 6H), 3.86 – 3.70 (m, 1H), 3.55 – 3.39 (m, 4H), 3.33 – 3.24 (m, 4H), 2.60 – 2.54 (m, 1H), 1.99 – 1.65 (m, 4H), 1.56 – 1.45 (m, 4H), 1.42 (s, 9H).	A
77		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.40 (t, J = 5.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.94 – 7.82 (m, 4H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 6.92 (t, J = 5.5 Hz, 1H), 3.93 – 3.86 (m, 6H), 3.31 – 3.25 (m, 2H), 3.15 – 3.07 (m, 2H), 1.39 (s, 9H).	C
78		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.81 (s, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.31 – 8.18 (m, 2H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.50 (d, J	B

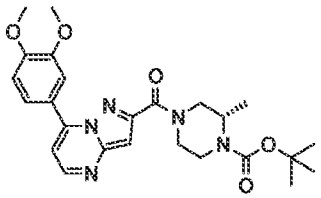
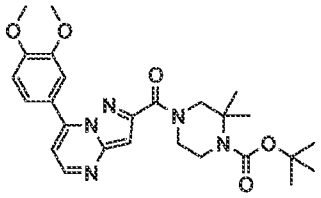
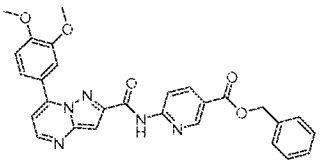
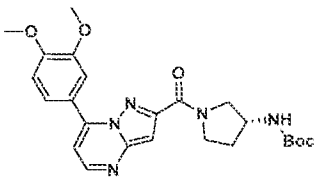
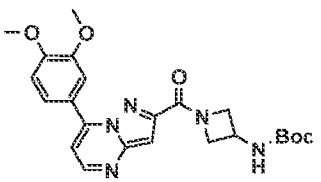
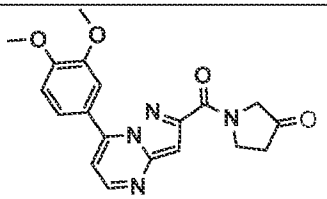
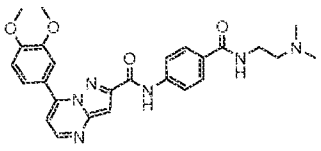
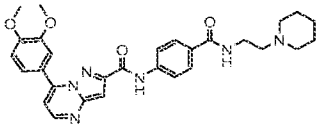
		= 4.5 Hz, 1H), 7.41 (s, 1H), 7.25 (d, J = 8.6 Hz, 1H), 3.95 – 3.89 (m, 6H).	
79		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.73 – 8.64 (m, 2H), 8.13 – 7.85 (m, 9H), 7.51 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.93 – 3.87 (m, 6H), 3.56 – 3.49 (m, 2H), 3.04 – 2.96 (m, 2H).	C
80		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.92 – 7.84 (m, 2H), 7.51 – 7.42 (m, 2H), 7.32 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.16 – 7.09 (m, 1H), 3.93 – 3.88 (m, 6H), 3.42 – 3.17 (m, 4H), 2.81 – 2.59 (m, 4H).	C
81		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.92 – 3.84 (m, 6H), 3.84 – 3.71 (m, 1H), 3.43 – 3.36 (m, 4H), 2.74 – 2.58 (m, 4H), 2.57 – 2.53 (m, 1H), 1.96 – 1.85 (m, 2H), 1.76 – 1.66 (m, 2H), 1.54 – 1.39 (m, 4H).	A
82		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.92 (dd, J = 8.5, 2.1 Hz, 1H), 7.88 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 4.5 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.16 (s, 1H), 4.11 – 4.03 (m, 1H), 3.92 – 3.86 (m, 6H), 3.43 – 3.36 (m, 4H), 2.74 – 2.58 (m, 5H), 1.91 – 1.82 (m, 2H), 1.73 – 1.62 (m, 4H), 1.59 – 1.48 (m, 2H).	A
83		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.5 Hz, 1H), 7.84 (t, J = 9.2 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.46 – 7.34 (m, 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.06 (s, 1H), 4.88 – 4.71 (m, 2H), 3.89 – 3.83 (m, 8H), 3.77 – 3.61 (m, 2H), 3.60 – 3.45 (m, 4H), 2.09 (s, 3H).	D
84		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.29 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.92 (dd, J = 8.5, 2.2 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.15 (s, 1H), 4.90 – 4.68 (m, 2H), 4.36 – 4.22 (m, 1H), 4.18 – 4.05 (m, 1H), 3.92 – 3.84 (m, 6H), 3.81 – 3.66 (m, 1H), 3.17 – 3.07 (m, 1H), 2.82 – 2.69 (m, 1H), 2.09 (s, 3H), 1.92 – 1.77 (m, 2H), 1.67 – 1.40 (m, 2H).	A
85		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 10.48 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.52 (d, J = 7.9 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.93 (s, 4H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.54 – 4.32 (m, 1H), 3.99 – 3.72 (m, 6H), 1.88 – 1.65 (m, 2H),	C

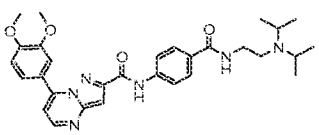
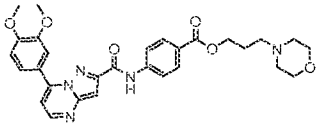
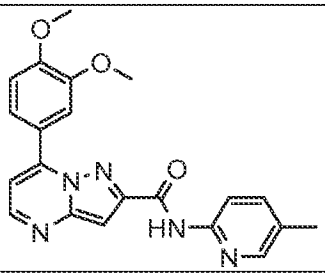
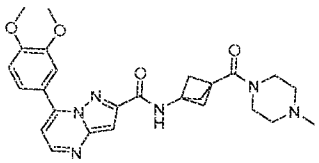
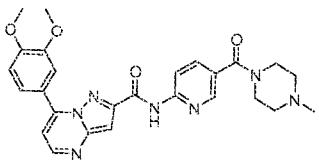
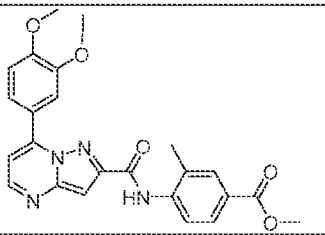
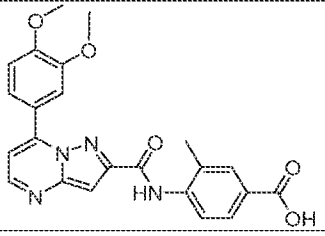
		1.65 – 1.51 (m, 1H), 0.94 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H).	
86		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.63 (s, 1H), 10.48 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.95 – 7.84 (m, 4H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.39 – 4.10 (m, 1H), 4.00 – 3.75 (m, 6H), 2.31 – 1.97 (m, 1H), 1.04 – 0.92 (m, 6H).	C
87		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 10.49 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.58 (d, J = 7.7 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.99 – 7.95 (m, 1H), 7.95 – 7.89 (m, 4H), 7.51 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.53 (dd, J = 14.4, 7.7 Hz, 1H), 3.96 – 3.85 (m, 6H), 2.67 – 2.53 (m, 2H), 2.12 – 2.03 (m, 5H).	C
88		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 2H), 10.49 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.66 (d, J = 7.4 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.98 – 7.85 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.29 – 7.14 (m, 1H), 4.81 – 4.53 (m, 1H), 4.01 – 3.70 (m, 6H), 2.93 – 2.79 (m, 1H), 2.78 – 2.57 (m, 1H).	C
89		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 10.48 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.59 (d, J = 7.2 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.95 – 7.86 (m, 4H), 7.51 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.7 Hz, 1H), 4.50 – 4.35 (m, 1H), 3.96 – 3.86 (m, 6H), 1.41 (d, J = 7.3 Hz, 3H).	C
90		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.5 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 4.4 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.06 (s, 1H), 4.68 (t, J = 5.4 Hz, 1H), 4.21 – 4.05 (m, 2H), 3.95 – 3.78 (m, 8H), 3.75 – 3.65 (m, 2H), 3.64 – 3.56 (m, 1H), 3.56 – 3.45 (m, 2H), 3.45 – 3.37 (m, 1H).	D
91		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.5, 2.1 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.14 (s, 1H), 4.53 (t, J = 5.4 Hz, 1H), 4.41 – 4.26 (m, 1H), 4.20 – 4.00 (m, 3H), 3.96 – 3.82 (m, 6H), 3.77 – 3.63 (m, 1H), 3.14 – 3.00 (m, 1H), 2.77 (t, J = 12.4 Hz, 1H), 1.84 (d, J = 11.8 Hz, 2H), 1.64 – 1.41 (m, 2H).	A

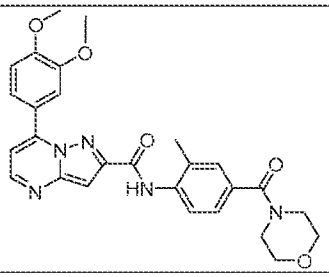
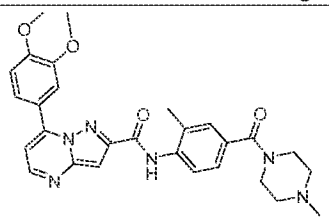
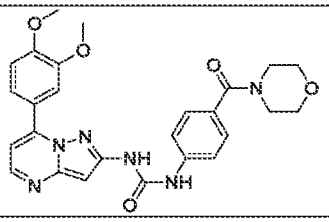
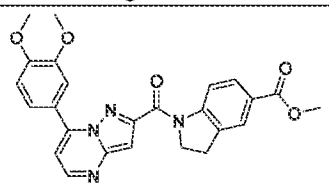
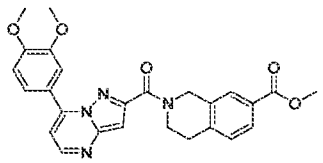
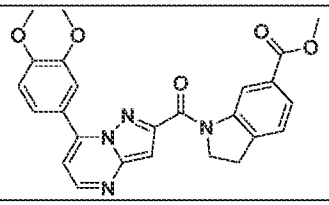
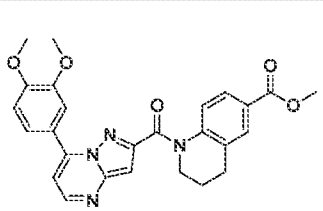
92		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.83 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 7.13 (s, 1H), 3.92 – 3.84 (m, 6H), 3.60 – 3.52 (m, 2H), 3.46 – 3.40 (m, 2H), 3.40 – 3.34 (m, 2H), 3.32 – 3.25 (m, 2H), 2.41 (s, 6H), 1.42 (s, 9H).	B
93		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.36 (s, 1H), 8.50 (d, J = 4.5 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.83 (dd, J = 8.5, 2.1 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.24 – 7.13 (m, 2H), 6.80 (s, 1H), 3.92 – 3.85 (m, 6H), 3.83 (s, 3H).	E
94		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 9.08 (t, J = 6.3 Hz, 1H), 8.66 (d, J = 4.5 Hz, 1H), 7.95 (dd, J = 8.5, 2.1 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 2.1 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.23 – 7.14 (m, 2H), 4.59 (d, J = 6.2 Hz, 2H), 3.90 – 3.84 (m, 6H).	A
95		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.98 (dd, J = 8.5, 2.2 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.32 (s, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.12 (s, 1H), 6.98 (s, 1H), 3.92 – 3.86 (m, 6H), 2.26 (s, 6H).	B
96		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.96 (dd, J = 8.5, 2.1 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.12 (s, 1H), 3.92 – 3.87 (m, 6H), 3.61 – 3.53 (m, 6H), 3.48 – 3.42 (m, 2H), 2.41 (s, 6H).	B
97		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.32 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.94 – 3.85 (m, 6H), 3.68 – 3.37 (m, 4H), 2.44 – 2.27 (m, 4H), 2.22 (s, 3H).	C
98		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.2 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.12 (s, 1H), 3.92 – 3.85 (m, 6H), 3.51 – 3.35 (m, 4H), 2.70 – 2.59 (m, 4H), 2.39 (s, 6H).	B

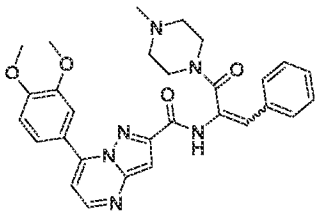
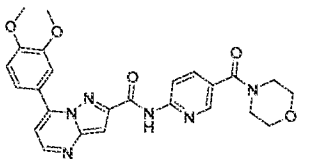
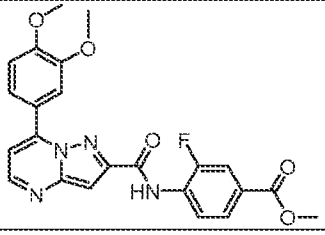
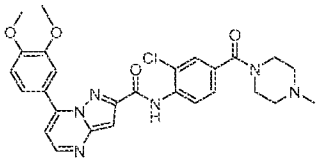
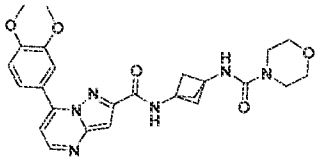
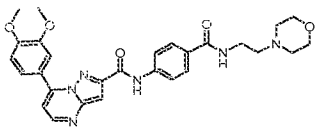
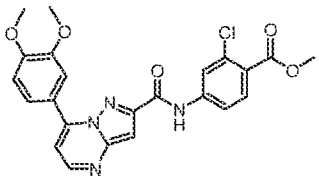
99		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 8.01 – 7.86 (m, 2H), 7.44 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.13 (s, 1H), 3.95 – 3.80 (m, 6H), 3.74 – 3.60 (m, 4H), 3.00 – 2.82 (m, 4H).	A
100		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.82 (dd, J = 8.5, 2.1 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 4.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 4.44 – 4.24 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.65 – 3.48 (m, 1H), 3.30 – 3.20 (m, 1H), 3.04 – 2.92 (m, 1H), 2.91 – 2.83 (m, 2H), 1.88 – 1.69 (m, 2H), 1.39 (s, 9H).	D
101		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.85 – 7.74 (m, 2H), 7.38 (d, J = 4.4 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.01 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 – 3.77 (m, 2H), 3.72 – 3.61 (m, 2H), 2.43 – 2.35 (m, 2H), 2.35 – 2.28 (m, 2H), 2.21 (s, 3H).	D
102		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.03 – 7.95 (m, 2H), 7.92 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.15 (s, 1H), 4.41 (d, J = 2.9 Hz, 1H), 3.93 – 3.79 (m, 7H), 3.79 – 3.71 (m, 1H), 1.88 – 1.72 (m, 2H), 1.72 – 1.46 (m, 6H).	A
103		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 8.5, 2.2 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 4.72 (s, 2H), 3.92 – 3.86 (m, 6H), 3.86 – 3.71 (m, 1H), 3.64 – 3.51 (m, 1H), 2.98 – 2.78 (m, 2H), 2.42 – 2.32 (m, 1H), 2.30 – 2.20 (m, 1H), 2.15 – 2.01 (m, 2H), 1.84 – 1.70 (m, 2H), 1.70 – 1.56 (m, 2H).	A
104		^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.81 (d, J = 8.7 Hz, 1H), 8.64 (d, J = 4.4 Hz, 1H), 8.13 (d, J = 1.9 Hz, 1H), 8.04 (dd, J = 8.6, 1.9 Hz, 1H), 7.78 (dd, J = 8.4, 2.1 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 7.45 (s, 1H), 7.12 – 7.07 (m, 2H), 4.04 (s, 3H), 4.01 (s, 3H), 3.95 (s, 3H).	B

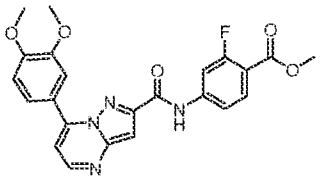
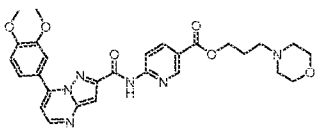
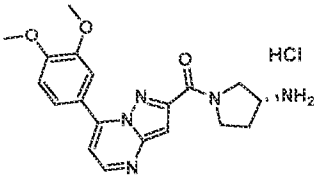
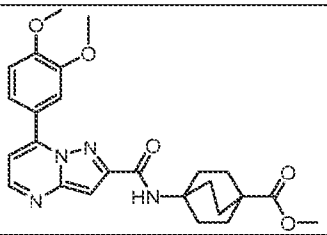
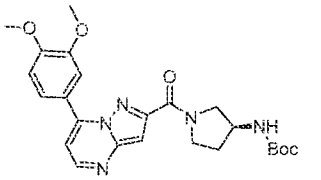
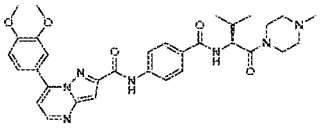
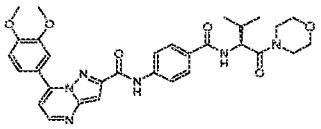
105		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.50 (s, 1H), 7.47 (d, J = 4.5 Hz, 1H), 7.40 – 7.36 (m, 3H), 7.25 (s, 1H), 7.17 (d, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H).	A
106		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.74 (d, J = 4.5 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 1.7 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.85 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.94 – 3.86 (m, 6H).	B
107		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.49 (s, 1H), 8.49 (d, J = 4.6 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.85 – 7.78 (m, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.22 – 7.16 (m, 2H), 6.80 (s, 1H), 3.91 – 3.85 (m, 6H).	E
108		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 9.88 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.50 (s, 1H), 7.47 (d, J = 4.5 Hz, 1H), 7.38 – 7.33 (m, 3H), 7.24 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H).	A
109		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.83 (s, 1H), 8.47 (d, J = 4.6 Hz, 1H), 7.83 (dd, J = 8.5, 2.1 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.21 – 7.13 (m, 2H), 6.91 – 6.84 (m, 2H), 6.73 (s, 1H), 3.99 (q, J = 7.0 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H).	E
110		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.5 Hz, 1H), 7.92 – 7.80 (m, 1H), 7.77 (s, 1H), 7.43 – 7.35 (m, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 3.98 – 3.44 (m, 14H), 2.12 – 1.89 (m, 1H), 0.85 – 0.59 (m, 4H).	D
111		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.5 Hz, 1H), 7.83 (dd, J = 8.5, 2.1 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 4.5 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.04 (s, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.93 – 3.78 (m, 8H), 3.74 – 3.61 (m, 2H), 3.53 – 3.46 (m, 2H), 3.44 – 3.37 (m, 2H), 1.20 (t, J = 6.8 Hz, 3H).	D

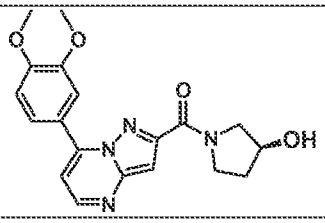
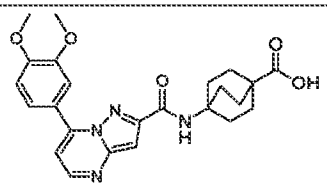
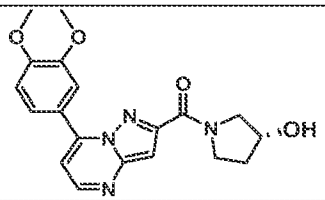
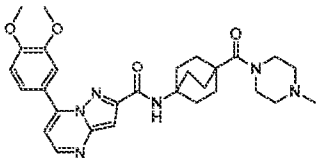
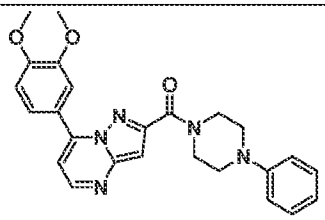
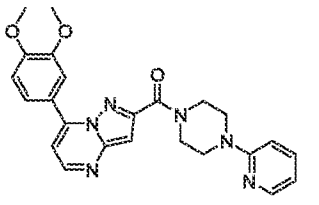
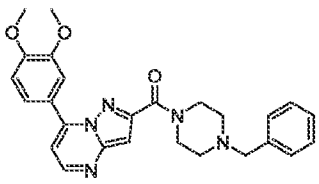
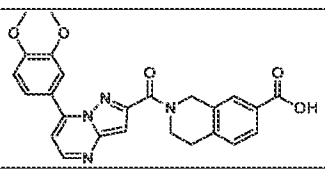
112		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 4.4 Hz, 1H), 7.87 – 7.64 (m, 2H), 7.39 (dd, J = 7.8, 4.5 Hz, 1H), 7.20 (dd, J = 8.4, 4.8 Hz, 1H), 7.05 (d, J = 21.4 Hz, 1H), 4.51 – 4.02 (m, 3H), 3.93 – 3.63 (m, 7H), 3.26 – 2.86 (m, 3H), 1.41 (d, J = 2.2 Hz, 9H), 1.05 (dd, J = 33.4, 6.7 Hz, 3H).	D
113		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 4.4 Hz, 1H), 7.95 – 7.66 (m, 2H), 7.38 (dd, J = 10.5, 4.4 Hz, 1H), 7.19 (dd, J = 11.7, 8.5 Hz, 1H), 7.07 (d, J = 28.1 Hz, 1H), 4.04 – 3.91 (m, 2H), 3.91 – 3.80 (m, 6H), 3.78 – 3.52 (m, 4H), 1.51 – 1.35 (m, 12H), 1.26 (s, 3H).	D
114		^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.98 (d, J = 1.5 Hz, 1H), 8.61 (d, J = 4.4 Hz, 1H), 8.49 (d, J = 8.7 Hz, 1H), 8.39 (dd, J = 8.7, 2.1 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.68 (dd, J = 8.4, 2.1 Hz, 1H), 7.56 – 7.33 (m, 6H), 7.10 (dd, J = 9.8, 6.4 Hz, 2H), 5.39 (s, 2H), 4.16 – 3.96 (m, 6H).	B
115		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (dd, J = 4.4, 1.2 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.38 (dd, J = 4.4, 1.2 Hz, 1H), 7.29 – 7.15 (m, 2H), 7.09 (d, J = 3.8 Hz, 1H), 4.13 – 3.95 (m, 2H), 3.90 – 3.82 (m, 6H), 3.77 – 3.37 (m, 3H), 2.16 – 1.97 (m, 1H), 1.89 – 1.74 (m, 1H), 1.46 – 1.28 (m, 9H).	D
116		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 4.4 Hz, 1H), 7.82 (dd, J = 8.3, 1.7 Hz, 1H), 7.74 (d, J = 1.4 Hz, 1H), 7.65 (d, J = 6.5 Hz, 1H), 7.40 (d, J = 4.4 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.10 (s, 1H), 4.89 – 4.68 (m, 1H), 4.46 – 4.26 (m, 3H), 3.95 – 3.82 (m, 7H), 1.39 (s, 9H).	D
117		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 – 8.62 (m, 1H), 7.87 – 7.68 (m, 2H), 7.44 – 7.36 (m, 1H), 7.24 – 7.13 (m, 2H), 4.46 (s, 1H), 4.40 (t, J = 7.8 Hz, 1H), 4.01 – 3.95 (m, 2H), 3.92 – 3.80 (m, 6H), 2.68 (t, J = 7.8 Hz, 1H), 2.61 (t, J = 8.0 Hz, 1H).	D
118		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.58 – 8.46 (m, 1H), 8.01 (dd, J = 8.5, 2.1 Hz, 1H), 7.98 – 7.84 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.32 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.92 – 3.86 (m, 6H), 3.58 – 3.48 (m, 2H), 3.07 – 2.94 (m, 2H), 2.65 (s, 6H).	C
119		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.35 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.98 – 7.84 (m, 5H), 7.51 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.96 – 3.86 (m,	C

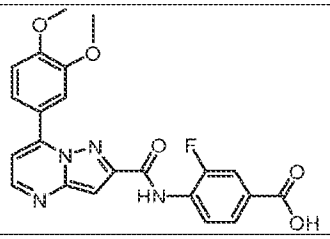
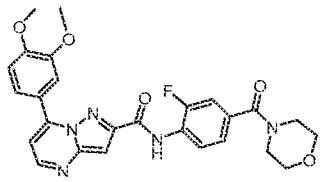
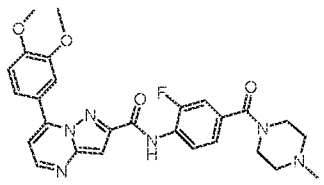
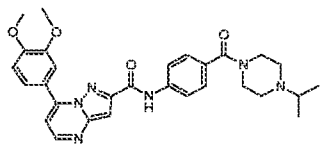
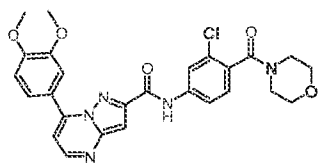
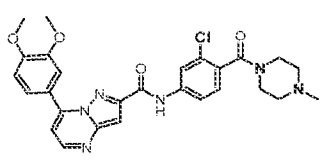
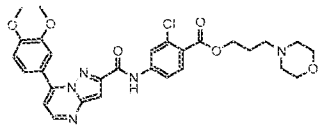
		6H), 3.73 – 3.41 (m, 4H), 3.01 – 2.78 (m, 2H), 1.84 – 1.32 (m, 8H).	
120		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.34 (s, 1H), 8.03 (d, J = 6.7 Hz, 1H), 8.00 – 7.74 (m, 5H), 7.50 (d, J = 4.4 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 4.05 – 3.72 (m, 6H), 3.29 – 3.10 (m, 2H), 3.10 – 2.85 (m, 2H), 1.25 – 0.74 (m, 12H).	C
121		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.07 – 7.88 (m, 6H), 7.51 (d, J = 4.5 Hz, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.31 (t, J = 6.4 Hz, 2H), 3.98 – 3.78 (m, 6H), 3.65 – 3.48 (m, 4H), 2.46 – 2.27 (m, 6H), 2.00 – 1.75 (m, 2H).	C
122		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.25 – 8.21 (m, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.95 (dd, J = 8.5, 2.1 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 8.5, 2.2 Hz, 1H), 7.49 (d, J = 4.5 Hz, 1H), 7.38 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 3.93 – 3.89 (m, 6H), 2.30 (s, 3H).	C
123		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.92 – 3.86 (m, 6H), 3.72 – 3.40 (m, 4H), 2.75 – 2.54 (m, 4H), 2.45 – 2.33 (m, 9H).	B
124		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.63 (d, J = 4.5 Hz, 1H), 8.38 – 8.34 (m, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.91 – 7.85 (m, 2H), 7.83 (d, J = 2.1 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.15 (d, J = 8.6 Hz, 1H), 3.87 – 3.80 (m, 6H), 3.61 – 3.28 (m, 4H), 2.35 – 2.18 (m, 4H), 2.12 (s, 3H).	B
125		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.92 – 7.82 (m, 3H), 7.50 (d, J = 4.5 Hz, 1H), 7.31 (s, 1H), 7.20 (d, J = 8.6 Hz, 1H), 3.92 – 3.82 (m, 9H), 2.38 (s, 3H).	B
126		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 9.84 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.0 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.91 – 7.81 (m, 3H), 7.50 (d, J = 4.5 Hz, 1H), 7.31 (s, 1H), 7.20 (d, J = 8.6 Hz, 1H), 3.93 – 3.86 (m, 6H), 2.37 (s, 3H).	B

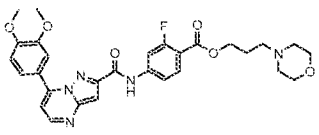
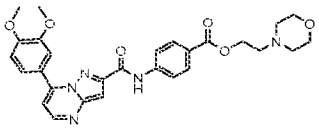
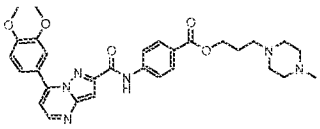
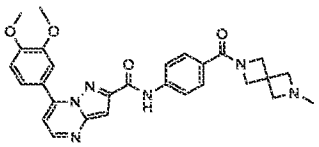
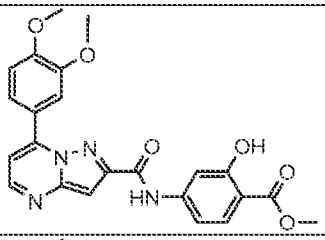
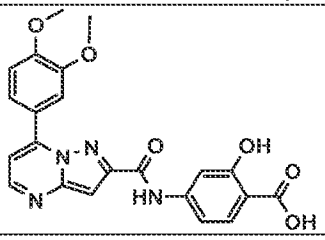
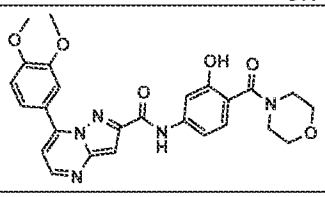
127		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 1.9 Hz, 1H), 7.86 (d, J = 2.1 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.37 (s, 1H), 7.34 – 7.28 (m, 2H), 7.20 (d, J = 8.6 Hz, 1H), 3.92 – 3.86 (m, 6H), 3.71 – 3.37 (m, 8H), 2.33 (s, 3H).	B
128		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 1.9 Hz, 1H), 7.86 (d, J = 2.1 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.36 – 7.25 (m, 3H), 7.20 (d, J = 8.6 Hz, 1H), 3.93 – 3.86 (m, 6H), 3.71 – 3.38 (m, 4H), 2.43 – 2.28 (m, 7H), 2.22 (s, 3H).	B
129		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.24 (s, 1H), 8.40 (d, J = 4.6 Hz, 1H), 7.80 – 7.68 (m, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.15 – 7.07 (m, 2H), 6.69 (s, 1H), 3.85 – 3.74 (m, 6H), 3.58 – 3.35 (m, 8H).	E
130		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 4.4 Hz, 1H), 8.50 – 8.33 (m, 1H), 8.03 – 7.93 (m, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.77 – 7.59 (m, 2H), 7.37 (s, 1H), 7.12 – 6.92 (m, 2H), 4.75 – 4.52 (m, 2H), 4.11 – 3.80 (m, 9H), 3.22 (t, J = 8.5 Hz, 2H).	D
131		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 – 8.61 (m, 1H), 7.95 – 7.65 (m, 4H), 7.48 – 7.30 (m, 2H), 7.19 (dd, J = 23.1, 8.6 Hz, 1H), 7.07 (d, J = 17.2 Hz, 1H), 5.17 (s, 1H), 4.92 (s, 1H), 4.05 (t, J = 5.8 Hz, 1H), 3.93 (t, J = 6.0 Hz, 1H), 3.90 – 3.71 (m, 9H), 3.05 – 2.88 (m, 2H).	D
132		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 7.94 – 7.79 (m, 2H), 7.74 (d, J = 7.1 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.28 (s, 1H), 7.22 (d, J = 8.7 Hz, 1H), 4.73 – 4.56 (m, 2H), 3.95 – 3.76 (m, 9H), 3.32 – 3.23 (m, 2H).	D
133		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.88 (d, J = 1.9 Hz, 1H), 7.58 (dd, J = 9.2, 1.9 Hz, 2H), 7.52 – 7.43 (m, 1H), 7.40 (d, J = 4.5 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.05 (s, 1H), 6.97 (d, J = 8.6 Hz, 1H), 4.00 – 3.90 (m, 2H), 3.89 – 3.71 (m, 9H), 2.90 (t, J = 6.6 Hz, 2H), 2.04 – 1.92 (m, 2H).	D

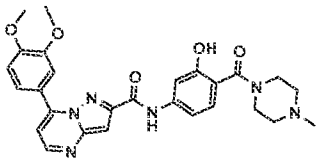
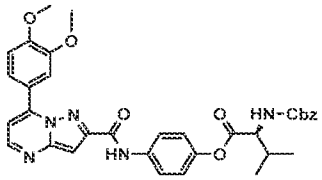
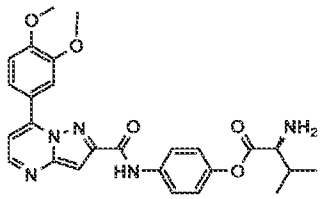
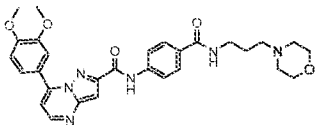
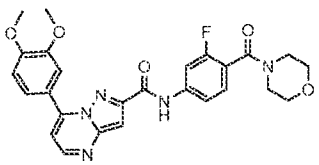
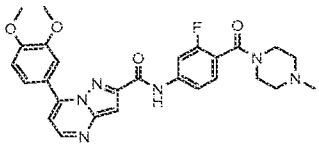
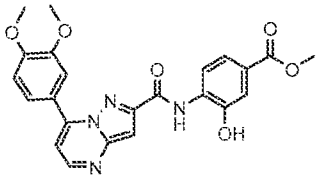
134		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.01 (dd, J = 8.5, 2.1 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.30 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.33 (s, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.70 – 3.48 (m, 4H), 2.42 – 2.32 (m, 4H), 2.22 (s, 3H).	A
135		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.50 – 8.46 (m, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.02 – 7.94 (m, 2H), 7.92 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.43 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 3.95 – 3.88 (m, 6H), 3.74 – 3.38 (m, 8H).	B
136		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.28 (t, J = 8.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.92 – 7.80 (m, 3H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 3.93 – 3.85 (m, 9H).	B
137		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.73 (d, J = 4.5 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 7.92 (dd, J = 8.5, 2.1 Hz, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.66 (d, J = 1.9 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 3.94 – 3.82 (m, 6H), 3.77 – 3.40 (m, 4H), 2.86 – 2.55 (m, 4H), 2.40 (s, 3H).	B
138		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.99 (dd, J = 8.5, 2.1 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.12 (s, 1H), 3.93 – 3.84 (m, 6H), 3.57 – 3.48 (m, 4H), 3.27 – 3.21 (m, 4H), 2.28 (s, 6H).	B
139		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.37 (t, J = 5.7 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.94 – 7.89 (m, 2H), 7.89 – 7.82 (m, 2H), 7.51 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.7 Hz, 1H), 3.93 - 3.87 (m, 6H), 3.61 – 3.55 (m, 4H), 3.44 – 3.35 (m, 2H), 2.50 – 2.38 (m, 6H).	C
140		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.17 (s, 1H), 8.03 (dd, J = 8.5, 2.2 Hz, 1H), 7.96 – 7.85 (m, 3H), 7.52 (d, J = 4.5 Hz, 1H), 7.35 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.95 – 3.88 (m, 6H), 3.86 (s, 3H).	B

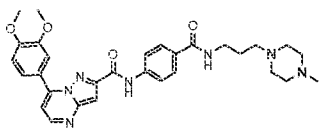
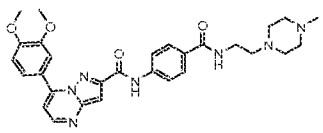
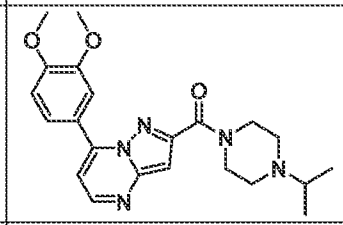
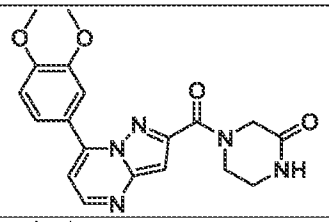
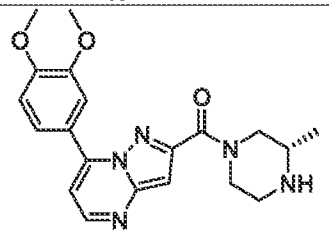
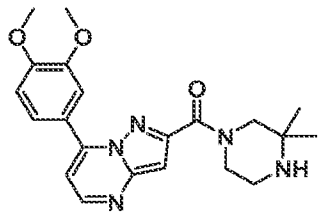
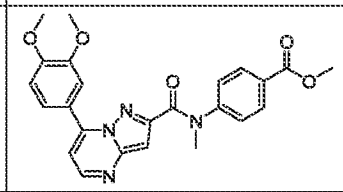
141		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 – 7.84 (m, 3H), 7.77 (dd, J = 8.7, 1.9 Hz, 1H), 7.52 (d, J = 4.5 Hz, 1H), 7.35 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.94 – 3.86 (m, 6H), 3.85 (s, 3H).	B
142		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.95 – 8.84 (m, 1H), 8.73 (d, J = 4.4 Hz, 1H), 8.46 – 8.29 (m, 2H), 8.00 – 7.83 (m, 2H), 7.52 (d, J = 4.5 Hz, 1H), 7.45 (s, 1H), 7.24 (d, J = 8.5 Hz, 1H), 4.35 (t, J = 6.5 Hz, 2H), 3.98 – 3.77 (m, 6H), 3.56 (t, J = 4.5 Hz, 4H), 2.43 (t, J = 7.1 Hz, 2H), 2.40 – 2.30 (m, 4H), 1.94 – 1.85 (m, 2H).	B
143		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (dd, J = 4.4, 2.5 Hz, 1H), 8.38 (s, 3H), 7.97 – 7.69 (m, 2H), 7.42 (dd, J = 13.9, 4.4 Hz, 1H), 7.25 (dd, J = 34.4, 8.8 Hz, 1H), 7.14 (s, 1H), 4.21 – 4.12 (m, 3H), 3.90 – 3.84 (m, 6H), 3.82 – 3.63 (m, 2H), 2.33 – 2.17 (m, 1H), 2.15 – 1.99 (m, 1H).	D
144		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 8.5, 2.1 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.19 (d, J = 8.6 Hz, 1H), 7.09 (s, 1H), 3.90 – 3.87 (m, 6H), 3.58 (s, 3H), 2.05 – 1.92 (m, 6H), 1.89 – 1.77 (m, 6H).	A
145		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 – 8.64 (m, 1H), 7.87 – 7.76 (m, 2H), 7.41 – 7.37 (m, 1H), 7.29 – 7.17 (m, 2H), 7.09 (d, J = 3.8 Hz, 1H), 4.16 – 4.03 (m, 2H), 3.90 – 3.82 (m, 6H), 3.81 – 3.50 (m, 3H), 2.13 – 2.00 (m, 1H), 1.92 – 1.78 (m, 1H), 1.45 – 1.35 (m, 9H).	D
146		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.43 (d, J = 8.6 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.99 – 7.87 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.71 (t, J = 8.6 Hz, 1H), 3.94 – 3.87 (m, 6H), 3.70 – 3.59 (m, 2H), 3.55 – 3.47 (m, 2H), 2.35 – 2.23 (m, 4H), 2.22 – 2.14 (m, 4H), 0.96 – 0.88 (m, 6H).	C
147		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.99 – 7.87 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.69 (t, J = 8.6 Hz, 1H), 3.93 – 3.88 (m, 6H), 3.73 – 3.64 (m, 2H), 3.62 – 3.47 (m, 6H), 2.26 – 2.10 (m, 1H), 1.00 – 0.89 (m, 6H).	C

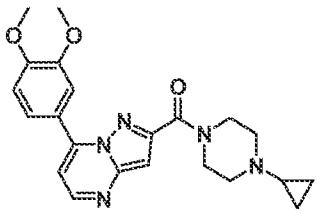
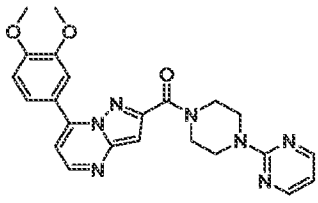
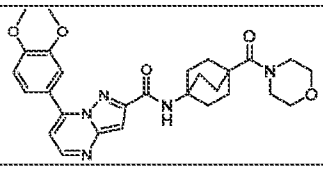
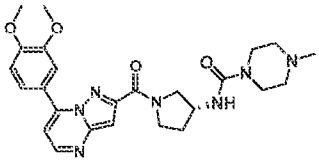
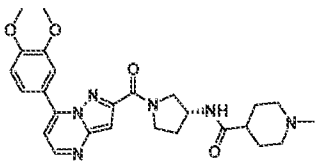
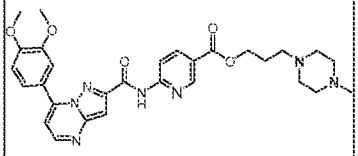
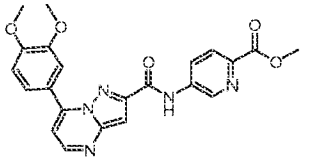
148		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 7.82 (s, 2H), 7.38 (s, 1H), 7.19 (s, 1H), 7.09 (s, 1H), 5.12 – 4.87 (m, 1H), 4.49 – 4.18 (m, 1H), 4.16 – 3.97 (m, 1H), 3.96 – 3.72 (m, 7H), 3.70 – 3.44 (m, 2H), 2.03 – 1.74 (m, 2H).	D
149		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 8.64 (d, J = 4.4 Hz, 1H), 8.10 – 7.93 (m, 1H), 7.90 – 7.78 (m, 1H), 7.52 – 7.34 (m, 2H), 7.20 (d, J = 8.6 Hz, 1H), 7.09 (s, 1H), 4.04 – 3.73 (m, 6H), 2.06 – 1.89 (m, 6H), 1.88 – 1.70 (m, 6H).	A
150		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 4.4 Hz, 1H), 7.93 – 7.74 (m, 2H), 7.39 (d, J = 4.3 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 3.0 Hz, 1H), 5.14 – 4.94 (m, 1H), 4.41 – 4.27 (m, 1H), 4.10 – 3.82 (m, 8H), 3.70 – 3.45 (m, 2H), 2.13 – 1.65 (m, 2H).	D
151		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 8.5, 2.1 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.20 (d, J = 8.6 Hz, 1H), 7.10 (s, 1H), 3.92 – 3.86 (m, 6H), 3.63 – 3.48 (m, 4H), 2.30 – 2.20 (m, 4H), 2.17 (s, 3H), 2.03 – 1.94 (m, 6H), 1.94 – 1.84 (m, 6H).	A
152		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.4 Hz, 1H), 7.85 (dd, J = 8.5, 2.1 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.41 (d, J = 4.5 Hz, 1H), 7.31 – 7.15 (m, 3H), 7.07 (s, 1H), 6.97 (d, J = 7.9 Hz, 2H), 6.82 (t, J = 7.3 Hz, 1H), 4.05 – 3.92 (m, 2H), 3.91 – 3.78 (m, 8H), 3.28 – 3.21 (m, 2H), 3.21 – 3.11 (m, 2H).	D
153		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.5 Hz, 1H), 8.16 – 8.09 (m, 1H), 7.85 (dd, J = 8.5, 2.1 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.65 – 7.50 (m, 1H), 7.41 (d, J = 4.5 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.07 (s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.75 – 6.62 (m, 1H), 4.00 – 3.91 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 – 3.75 (m, 2H), 3.70 – 3.59 (m, 2H), 3.59 – 3.47 (m, 2H).	D
154		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.85 – 7.72 (m, 2H), 7.42 – 7.30 (m, 5H), 7.30 – 7.24 (m, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.01 (s, 1H), 3.88 (s, 3H), 3.86 – 3.75 (m, 5H), 3.74 – 3.64 (m, 2H), 3.52 (s, 2H), 2.47 – 2.42 (m, 2H), 2.42 – 2.36 (m, 2H).	D
155		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.74 – 8.55 (m, 1H), 7.93 – 7.73 (m, 4H), 7.40 (t, J = 3.8 Hz, 1H), 7.33 (dd, J = 7.8, 4.5 Hz, 1H), 7.27 – 7.14 (m, 1H), 7.07 (d, J = 12.2 Hz, 1H), 5.21 (s, 1H), 4.90 (s,	D

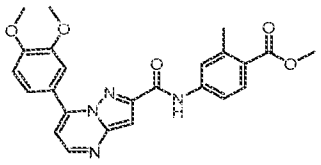
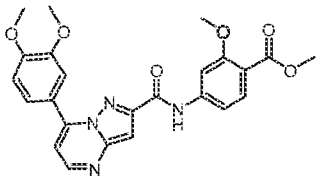
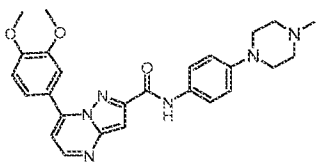
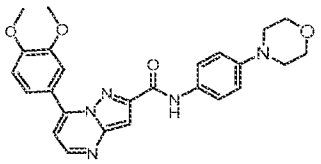
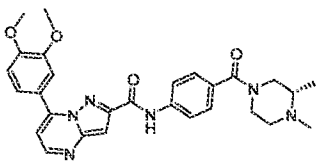
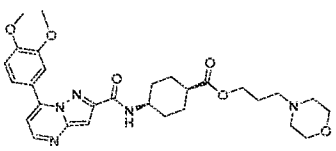
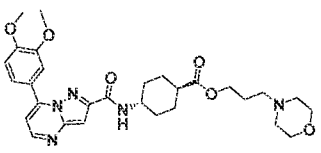
		1H), 4.04 (t, J = 5.8 Hz, 1H), 3.93 (t, J = 5.8 Hz, 1H), 3.85 (m, 6H), 3.02 – 2.92 (m, 2H).	
156		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.20 (t, J = 8.1 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.90 (dd, J = 8.4, 2.0 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.78 (dd, J = 11.3, 1.6 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.93 – 3.88 (m, 6H).	B
157		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.08 (t, J = 8.0 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 8.5, 2.0 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.45 (dd, J = 10.9, 1.7 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.21 (d, J = 8.6 Hz, 1H), 3.94 – 3.87 (m, 6H), 3.72 – 3.38 (m, 8H).	B
158		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.07 (t, J = 8.0 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 8.5, 2.0 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.42 (dd, J = 10.8, 1.7 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.21 (d, J = 8.6 Hz, 1H), 3.92 – 3.87 (m, 6H), 3.72 – 3.39 (m, 4H), 2.44 – 2.27 (m, 4H), 2.22 (s, 3H).	B
159		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 4.5 Hz, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.94 – 3.88 (m, 6H), 3.71 – 3.39 (m, 4H), 2.75 – 2.65 (m, 1H), 2.50 – 2.38 (m, 4H), 1.07 – 0.91 (m, 6H).	C
160		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.10 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.94 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.99 - 3.84 (m, 6H), 3.75 – 3.61 (m, 4H), 3.60 – 3.50 (m, 2H), 3.24 – 3.13 (m, 2H).	B
161		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.10 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.95 - 3.84 (m, 6H), 3.76 – 3.51 (m, 2H), 3.23 – 3.08 (m, 2H), 2.47 – 2.38 (m, 2H), 2.38 – 2.29 (m, 2H), 2.29 – 2.14 (m, 3H).	B
162		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.15 (s, 1H), 8.01 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 – 7.83 (m, 3H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.30 (t, J = 6.4	B

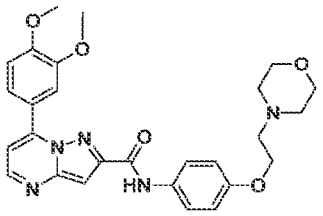
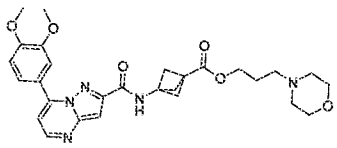
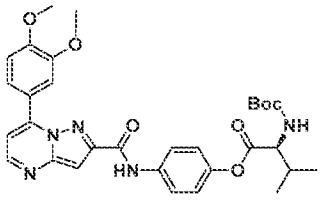
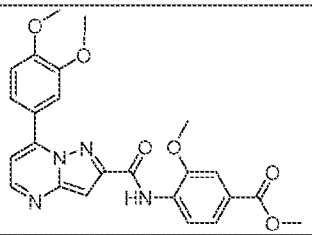
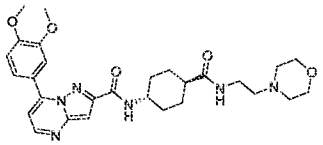
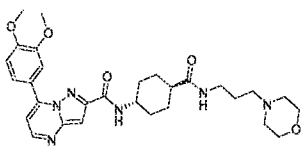
		Hz, 2H), 3.98 - 3.78 (m, 6H), 3.56 (t, J = 4.5 Hz, 4H), 2.42 (t, J = 7.0 Hz, 2H), 2.40 – 2.28 (m, 4H), 1.91 – 1.78 (m, 2H).	
163		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.98 – 7.85 (m, 3H), 7.77 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 4.4 Hz, 1H), 7.36 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.31 (t, J = 6.4 Hz, 2H), 3.96 - 3.81 (m, 6H), 3.63 – 3.47 (m, 4H), 2.45 – 2.26 (m, 6H), 1.97 – 1.75 (m, 2H).	B
164		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.08 – 7.90 (m, 6H), 7.51 (d, J = 4.4 Hz, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 4.38 (t, J = 5.6 Hz, 2H), 3.99 - 3.83 (m, 6H), 3.65 – 3.49 (m, 4H), 2.70 (t, J = 5.8 Hz, 2H), 2.49 – 2.36 (m, 4H).	C
165		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 8.71 (d, J = 4.3 Hz, 1H), 8.11 – 7.83 (m, 6H), 7.51 (d, J = 4.4 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.29 (t, J = 6.3 Hz, 2H), 3.97 - 3.87 (m, 6H), 2.50 – 2.21 (m, 10H), 2.16 (s, 3H), 1.94 – 1.74 (m, 2H).	C
166		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.41 (s, 2H), 4.12 (d, J = 19.2 Hz, 2H), 3.95 – 3.86 (m, 6H), 3.26 (s, 4H), 2.17 (s, 3H).	C
167		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 – 10.48 (m, 2H), 8.71 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.41 (dd, J = 8.8, 2.0 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.93 – 3.87 (m, 9H).	B
168		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.79 (s, 1H), 11.47 (s, 1H), 10.50 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.43 – 7.31 (m, 2H), 7.23 (d, J = 8.6 Hz, 1H), 3.93 – 3.87 (m, 6H).	B
169		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 10.03 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.58 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.31 (s, 1H), 7.25 – 7.19 (m, 2H), 7.14 (d, J = 8.3 Hz, 1H), 3.93 – 3.88 (m, 6H), 3.68 – 3.36 (m, 8H).	B

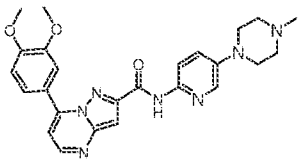
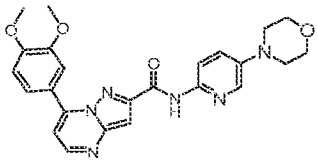
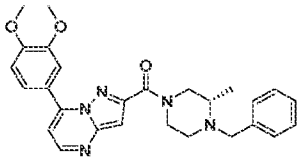
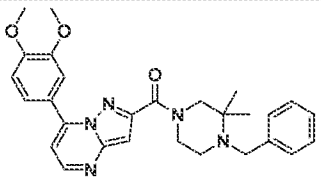
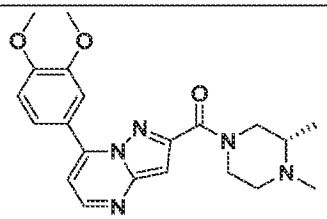
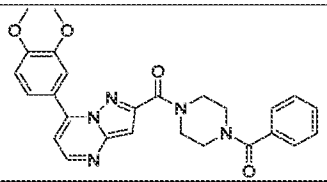
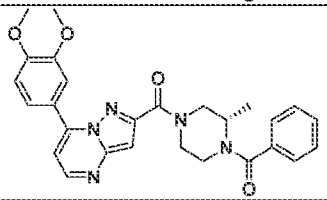
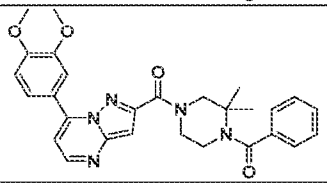
170		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.97 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.03 – 7.95 (m, 2H), 7.57 (d, J = 1.8 Hz, 1H), 7.50 (d, J = 4.5 Hz, 1H), 7.31 (s, 1H), 7.22 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.3 Hz, 1H), 3.94 – 3.87 (m, 6H), 3.65 – 3.35 (m, 4H), 2.38 – 2.24 (m, 4H), 2.19 (s, 3H).	B
171		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.0 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.86 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.42 – 7.30 (m, 6H), 7.22 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 8.9 Hz, 2H), 5.12 – 5.07 (m, 2H), 4.20 – 4.14 (m, 1H), 3.94 – 3.87 (m, 6H), 2.30 – 2.14 (m, 1H), 1.03 (d, J = 6.7 Hz, 6H).	C
172		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.0 Hz, 1H), 7.96 (s, 1H), 7.86 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.31 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.13 (d, J = 8.9 Hz, 2H), 3.93 – 3.88 (m, 6H), 3.73 – 3.71 (m, 1H), 2.09 – 1.98 (m, 1H), 1.94 – 1.78 (m, 2H), 1.01 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H).	C
173		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.50 – 8.36 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.99 – 7.77 (m, 5H), 7.51 (d, J = 4.4 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.02 – 3.77 (m, 6H), 3.64 – 3.47 (m, 4H), 3.31 – 3.22 (m, 2H), 2.44 – 2.18 (m, 6H), 1.76 – 1.58 (m, 2H).	C
174		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 8.71 (d, J = 4.3 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.89 (d, J = 12.3 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 4.2 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.7 Hz, 1H), 3.95 – 3.80 (m, 6H), 3.73 – 3.58 (m, 4H), 3.60 – 3.46 (m, 2H), 3.32 – 3.20 (m, 2H).	B
175		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.95 (s, 1H), 7.89 (d, J = 12.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.96 – 3.86 (m, 6H), 3.74 – 3.55 (m, 2H), 3.31 – 3.22 (m, 2H), 2.47 – 2.39 (m, 2H), 2.39 – 2.30 (m, 2H), 2.26 (s, 3H).	B
176		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.82 (s, 1H), 8.72 (d, J = 4.3 Hz, 1H), 8.48 (d, J = 8.3 Hz, 1H), 8.00 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.57 – 7.38 (m, 3H), 7.31 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 3.95 - 3.85 (m, 6H), 3.82 (s, 3H).	B

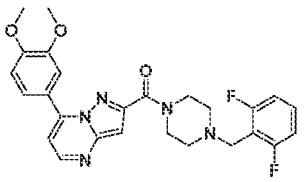
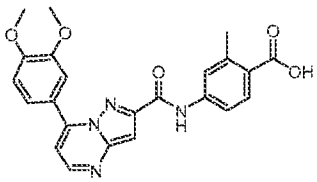
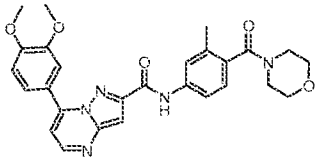
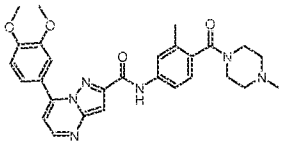
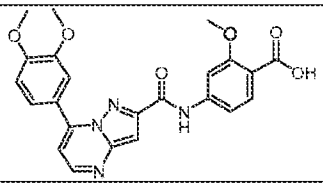
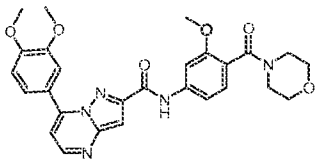
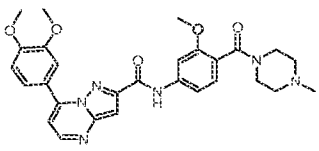
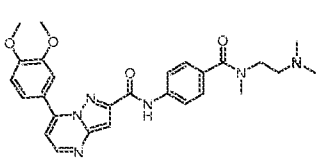
177		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.57 – 8.36 (m, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.98 – 7.75 (m, 5H), 7.50 (d, J = 4.4 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.7 Hz, 1H), 3.98 – 3.79 (m, 6H), 3.31 – 3.20 (m, 2H), 2.50 – 2.27 (m, 10H), 2.24 (s, 3H), 1.75 – 1.58 (m, 2H).	C
178		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.70 (d, J = 4.0 Hz, 1H), 8.40 - 8.32 (m, 1H), 8.10 - 7.70 (m, 6H), 7.51 (d, J = 3.5 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 4.0 - 3.8 (m, 6H), 3.42 - 3.36 (m, 2H), 2.48 - 2.00 (m, 13H).	C
179		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.86 – 7.72 (m, 2H), 7.38 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.00 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 – 3.71 (m, 2H), 3.71 – 3.59 (m, 2H), 2.77 – 2.60 (m, 1H), 2.46 – 2.39 (m, 2H), 0.97 (d, J = 6.5 Hz, 6H).	D
180		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.4 Hz, 1H), 8.21 – 8.07 (m, 1H), 7.88 – 7.69 (m, 2H), 7.45 – 7.32 (m, 1H), 7.26 – 7.13 (m, 1H), 7.09 (d, J = 8.9 Hz, 1H), 4.55 (s, 1H), 4.17 (s, 1H), 4.10 – 3.97 (m, 1H), 3.92 – 3.72 (m, 7H), 3.32 – 3.21 (m, 2H).	D
181		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.4 Hz, 1H), 7.87 – 7.69 (m, 2H), 7.44 – 7.32 (m, 1H), 7.18 (t, J = 8.3 Hz, 1H), 6.99 (s, 1H), 4.43 – 4.18 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.15 – 2.90 (m, 1H), 2.87 – 2.56 (m, 4H), 2.47 – 2.36 (m, 1H), 1.05 – 0.80 (m, 3H).	D
182		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (dd, J = 4.4, 2.0 Hz, 1H), 7.85 – 7.70 (m, 2H), 7.37 (dd, J = 11.6, 4.5 Hz, 1H), 7.18 (t, J = 8.4 Hz, 1H), 6.98 (d, J = 20.0 Hz, 1H), 3.90 – 3.83 (m, 6H), 3.68 – 3.59 (m, 1H), 3.59 – 3.52 (m, 1H), 3.51 (s, 1H), 3.40 (s, 1H), 2.85 – 2.70 (m, 2H), 2.27 – 1.95 (m, 1H), 1.06 (s, 3H), 0.93 (s, 3H).	D
183		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 4.5 Hz, 1H), 7.98 – 7.84 (m, 2H), 7.47 – 7.35 (m, 3H), 7.32 (d, J = 4.5 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.96 (s, 1H), 6.86 (d, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.85 – 3.77 (m, 6H), 3.48 (s, 3H).	B

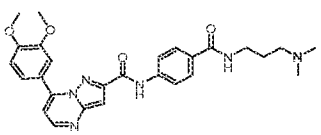
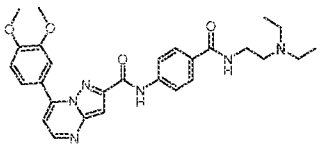
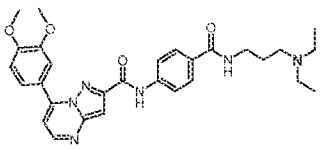
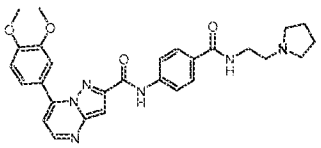
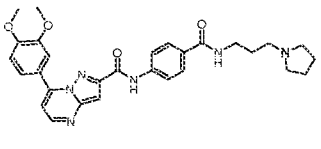
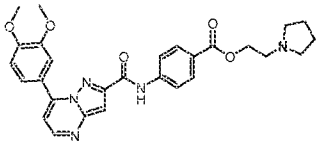
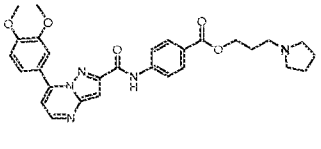
184		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.38 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.01 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.78 – 3.70 (m, 2H), 3.69 – 3.58 (m, 2H), 2.65 – 2.57 (m, 2H), 2.55 – 2.52 (m, 2H), 1.71 – 1.57 (m, 1H), 0.48 – 0.40 (m, 2H), 0.37 – 0.28 (m, 2H).	D
185		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.4 Hz, 1H), 8.40 (d, J = 4.7 Hz, 2H), 7.88 – 7.81 (m, 1H), 7.79 (s, 1H), 7.40 (d, J = 4.5 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.07 (s, 1H), 6.68 (t, J = 4.7 Hz, 1H), 3.97 – 3.90 (m, 2H), 3.89 – 3.81 (m, 8H), 3.81 – 3.69 (m, 4H).	D
186		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.4 Hz, 1H), 8.02 (s, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.53 – 7.39 (m, 2H), 7.20 (d, J = 8.6 Hz, 1H), 7.10 (s, 1H), 3.96 – 3.86 (m, 6H), 3.62 – 3.51 (m, 8H), 2.05 – 1.87 (m, 12H).	A
187		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 3.2 Hz, 1H), 7.90 – 7.75 (m, 2H), 7.39 (d, J = 4.3 Hz, 1H), 7.20 (t, J = 8.3 Hz, 1H), 7.10 (d, J = 3.1 Hz, 1H), 6.73 – 6.53 (m, 1H), 4.33 – 4.11 (m, 2H), 4.09 – 3.99 (m, 1H), 3.94 – 3.80 (m, 6H), 3.80 – 3.64 (m, 2H), 3.61 – 3.39 (m, 4H), 2.48 – 2.33 (m, 4H), 2.31 – 2.20 (m, 3H), 2.13 – 2.01 (m, 1H), 1.96 – 1.83 (m, 1H).	D
188		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 3.0 Hz, 1H), 8.20 – 8.00 (m, 1H), 7.89 – 7.67 (m, 2H), 7.47 – 7.36 (m, 1H), 7.28 – 7.15 (m, 1H), 7.10 (d, J = 5.9 Hz, 1H), 4.36 – 4.22 (m, 1H), 4.21 – 3.98 (m, 2H), 3.84 (s, 6H), 3.80 – 3.54 (m, 2H), 2.80 – 2.67 (m, 2H), 2.11 (d, J = 3.4 Hz, 3H), 2.08 – 1.90 (m, 2H), 1.91 – 1.69 (m, 3H), 1.66 – 1.43 (m, 4H).	D
189		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.92 (s, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.49 – 8.27 (m, 2H), 8.03 – 7.82 (m, 2H), 7.51 (d, J = 4.4 Hz, 1H), 7.44 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 4.33 (t, J = 6.5 Hz, 2H), 3.99 - 3.81 (m, 6H), 2.49 – 2.18 (m, 10H), 2.13 (s, 3H), 1.95 – 1.81 (m, 2H).	B
190		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 9.12 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.51 (d, J = 4.4 Hz, 1H), 7.37 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.98 – 3.83 (m, 9H).	B

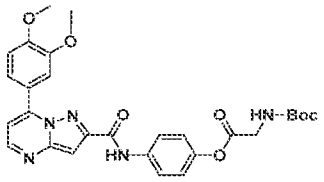
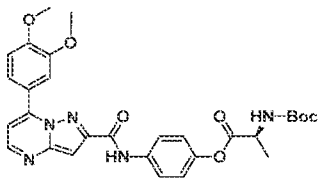
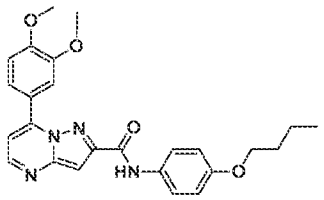
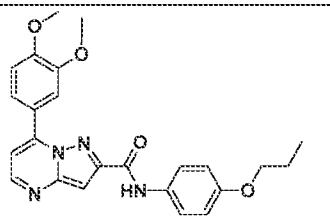
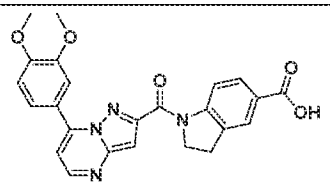
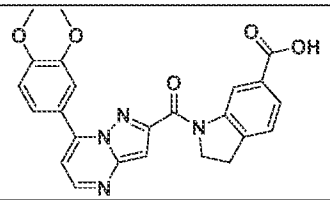
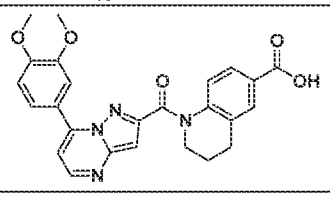
191		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.85 – 7.74 (m, 2H), 7.50 (d, J = 4.4 Hz, 1H), 7.33 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.97 - 3.86 (m, 6H), 3.82 (s, 3H), 2.55 (s, 3H).	B
192		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.10 – 7.86 (m, 2H), 7.83 – 7.64 (m, 2H), 7.64 – 7.40 (m, 2H), 7.33 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 3.97 – 3.87 (m, 6H), 3.83 (s, 3H), 3.77 (s, 3H).	B
193		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 6.8 Hz, 1H), 7.95 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 4.4 Hz, 1H), 7.26 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.98 – 3.76 (m, 6H), 3.22 – 3.01 (m, 4H), 2.58 – 2.52 (m, 4H), 2.28 (s, 3H).	C
194		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.0 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 4.5 Hz, 1H), 7.26 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 9.0 Hz, 2H), 3.97 - 3.82 (m, 6H), 3.82 – 3.70 (m, 4H), 3.13 – 2.97 (m, 4H).	C
195		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.33 (s, 1H), 7.22 (d, J = 8.7 Hz, 1H), 4.35 – 4.07 (m, 1H), 3.96 – 3.87 (m, 6H), 3.69 – 3.42 (m, 1H), 3.08 – 2.58 (m, 3H), 2.34 – 1.91 (m, 5H), 1.14 – 0.86 (m, 3H).	C
196		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.2 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.14 (s, 1H), 4.09 (t, J = 6.5 Hz, 2H), 3.96 – 3.85 (m, 7H), 3.59 – 3.51 (m, 4H), 2.62 – 2.55 (m, 1H), 2.40 – 2.25 (m, 6H), 2.01 – 1.88 (m, 2H), 1.80 – 1.57 (m, 8H).	A
197		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 4.06 (t, J = 6.2 Hz, 2H), 3.94 – 3.83 (m, 6H), 3.85 – 3.72 (m, 1H), 3.62 – 3.51 (m, 4H), 2.41 – 2.22 (m, 7H), 2.01 – 1.85 (m, 4H), 1.80 – 1.67 (m, 2H), 1.54 – 1.38 (m, 4H).	A

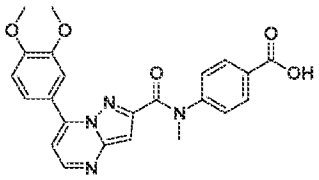
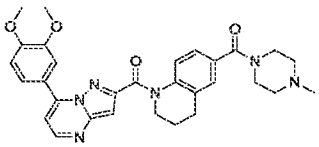
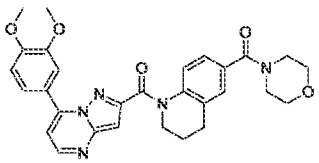
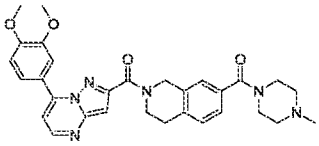
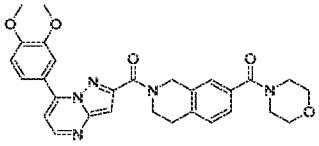
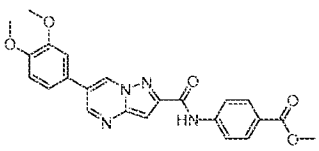
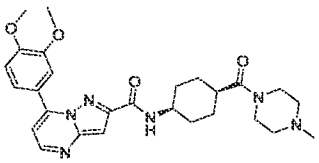
198		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 9.1 Hz, 2H), 4.08 (t, J = 5.8 Hz, 2H), 3.94 – 3.86 (m, 6H), 3.63 – 3.54 (m, 4H), 2.69 (t, J = 5.8 Hz, 2H), 2.49 – 2.44 (m, 4H).	C
199		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.12 (s, 1H), 4.08 (t, J = 6.6 Hz, 2H), 3.90 – 3.85 (m, 6H), 3.61 – 3.51 (m, 4H), 2.40 – 2.26 (m, J = 8.1 Hz, 12H), 1.80 – 1.70 (m, 2H).	B
200		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.30 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 8.9 Hz, 2H), 4.10 – 4.01 (m, 1H), 3.94 – 3.85 (m, 6H), 2.23 – 2.14 (m, 1H), 1.42 (s, 9H), 1.01 (d, J = 6.8 Hz, 6H).	C
201		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.73 (d, J = 4.4 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 8.4, 2.1 Hz, 1H), 7.69 (dd, J = 8.4, 1.7 Hz, 1H), 7.59 (d, J = 1.7 Hz, 1H), 7.49 (d, J = 4.4 Hz, 1H), 7.31 (s, 1H), 7.26 (d, J = 8.6 Hz, 1H), 3.99 – 3.84 (m, 12H).	B
202		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.2 Hz, 1H), 7.70 (t, J = 5.7 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.92 – 3.86 (m, 6H), 3.83 – 3.72 (m, 1H), 3.59 – 3.52 (m, 4H), 3.20 – 3.12 (m, 2H), 2.40 – 2.28 (m, 6H), 2.12 – 2.02 (m, 1H), 1.92 – 1.84 (m, 2H), 1.82 – 1.73 (m, 2H), 1.53 – 1.37 (m, 4H).	A
203		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.85 – 7.77 (m, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.91 – 3.87 (m, 6H), 3.83 – 3.71 (m, 1H), 3.69 – 3.51 (m, 4H), 3.11 – 3.02 (m, 2H), 2.50 – 2.29 (m, 6H), 2.11 – 2.01 (m, 1H), 1.93 – 1.85 (m, 2H), 1.82 – 1.72 (m, 2H), 1.65 – 1.53 (m, 2H), 1.53 – 1.36 (m, 4H).	A

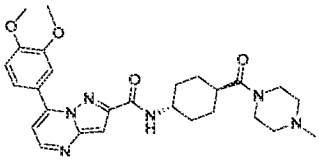
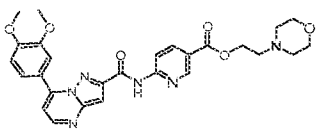
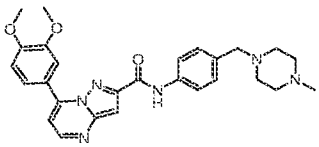
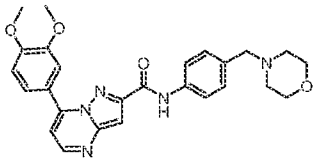
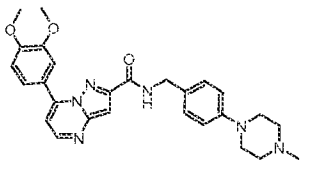
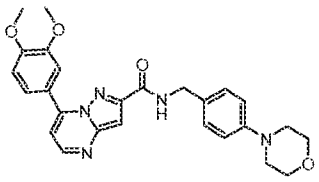
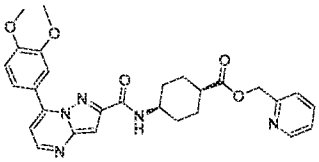
204		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.12 – 8.00 (m, 2H), 7.95 (d, J = 8.4 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.56 – 7.42 (m, 2H), 7.34 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 3.95 – 3.85 (m, 6H), 3.21 – 3.12 (m, 4H), 2.48 – 2.44 (m, 4H), 2.23 (s, 3H).	C
205		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.15 – 8.03 (m, 2H), 7.95 (d, J = 8.5 Hz, 1H), 7.93 – 7.82 (m, 1H), 7.63 – 7.43 (m, 2H), 7.35 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 3.99 – 3.82 (m, 6H), 3.80 – 3.67 (m, 4H), 3.20 – 3.07 (m, 4H).	B
206		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 – 8.60 (m, 1H), 7.83 – 7.76 (m, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.40 – 7.28 (m, 5H), 7.28 – 7.22 (m, 1H), 7.17 (t, J = 8.2 Hz, 1H), 7.00 (d, J = 2.8 Hz, 1H), 4.21 – 3.74 (m, 9H), 3.51 – 3.42 (m, 1H), 3.32 – 3.22 (m, 2H), 3.15 – 3.03 (m, 1H), 2.75 – 2.57 (m, 1H), 2.20 – 2.09 (m, 1H), 1.19 – 0.97 (m, 3H).	D
207		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 – 8.59 (m, 1H), 7.84 – 7.69 (m, 2H), 7.40 – 7.27 (m, 5H), 7.27 – 7.11 (m, 2H), 7.01 (d, J = 7.3 Hz, 1H), 3.93 – 3.76 (m, 6H), 3.76 – 3.55 (m, 3H), 3.54 – 3.41 (m, 3H), 2.44 – 2.35 (m, 2H), 1.15 (s, 3H), 1.01 (s, 3H).	D
208		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.4 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.38 – 7.36 (m, 1H), 7.21 – 7.16 (m, 1H), 7.01 (s, 1H), 4.33 – 4.25 (m, 2H), 3.88 (s, 3H), 3.86 (s,3H) 3.09 – 2.95 (m, 1H), 2.84 – 2.66 (m, 2H), 2.20 (s, 3H), 2.15 – 2.01 (m, 2H), 1.07 – 0.90 (m, 3H).	D
209		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 4.1 Hz, 1H), 8.01 – 7.66 (m, 2H), 7.54 – 7.31 (m, 6H), 7.28 – 7.09 (m, 1H), 7.05 (s, 1H), 4.03 – 3.56 (m, 12H), 3.56 – 3.40 (m, 2H).	D
210		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 - 8.54 (m, 1H), 7.75 - 7.55 (m, 2H), 7.49 - 7.34 (m, 5H), 7.17 (d, J = 7.4 Hz, 1H), 7.07 - 6.96 (m, 2H), 4.98 - 4.47 (m, 3H), 4.05 - 3.79 (m, 7H), 3.54 - 2.83 (m, 3H), 1.38 - 1.14 (m, 3H).	D
211		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 – 8.60 (m, 1H), 7.88 – 7.67 (m, 2H), 7.51 – 7.31 (m, 6H), 7.24 – 7.00 (m, 2H), 4.14 – 3.77 (m, 8H), 3.71 – 3.48 (m, 4H), 1.64 – 1.35 (m, 6H).	D

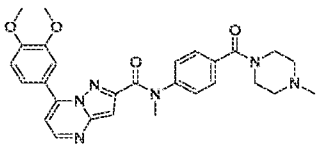
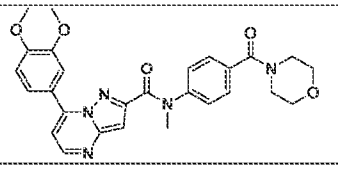
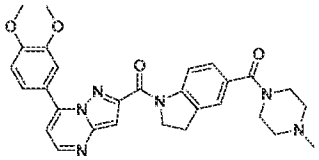
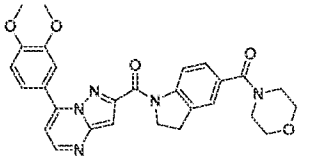
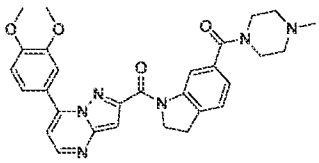
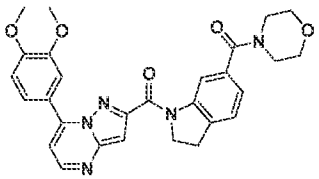
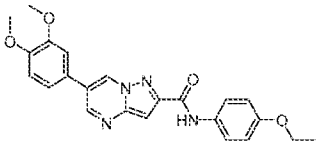
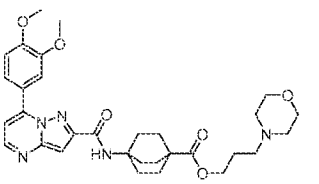
212		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.82 (dd, J = 8.5, 2.1 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.49 – 7.39 (m, 1H), 7.38 (d, J = 4.5 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.15 – 7.05 (m, 2H), 7.00 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.82 – 3.74 (m, 2H), 3.71 – 3.57 (m, 4H), 2.50 – 2.45 (m, 2H), 2.46 – 2.38 (m, 2H).	D
213		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 – 12.43 (m, 1H), 10.42 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.94 (s, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.82 – 7.73 (m, 2H), 7.53 – 7.46 (m, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.1 Hz, 1H), 3.96 – 3.85 (m, 6H), 2.55 (s, 3H).	B
214		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.69 (d, J = 4.4 Hz, 1H), 8.08 – 7.99 (m, 1H), 7.99 – 7.87 (m, 1H), 7.81 – 7.64 (m, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.30 (s, 1H), 7.21 (t, J = 8.5 Hz, 2H), 3.98 – 3.81 (m, 6H), 3.65 (s, 4H), 3.56 – 3.43 (m, 2H), 3.23 – 3.08 (m, 2H), 2.24 (s, 3H).	B
215		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.69 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.94 (s, 1H), 7.77 – 7.63 (m, 2H), 7.49 (d, J = 4.4 Hz, 1H), 7.30 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 3.99 – 3.82 (m, 6H), 3.74 – 3.53 (m, 2H), 3.20 – 3.08 (m, 2H), 2.41 – 2.29 (m, 2H), 2.26 – 2.13 (m, 8H).	B
216		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.70 (d, J = 3.7 Hz, 1H), 8.08 – 7.90 (m, 2H), 7.86 – 7.62 (m, 2H), 7.60 – 7.45 (m, 2H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.96 - 3.87 (m, 6H), 3.83 (s, 3H).	B
217		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.15 – 7.88 (m, 2H), 7.67 (s, 1H), 7.59 – 7.41 (m, 2H), 7.32 (s, 1H), 7.28 – 7.10 (m, 2H), 4.01 – 3.85 (m, 6H), 3.82 (s, 3H), 3.69 – 3.58 (m, 4H), 3.57 – 3.50 (m, 2H), 3.25 – 3.05 (m, 2H).	B
218		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.07 – 7.87 (m, 2H), 7.66 (s, 1H), 7.50 (d, J = 4.6 Hz, 2H), 7.31 (s, 1H), 7.22 (d, J = 9.2 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 3.93 - 3.88 (m, 6H), 3.80 (s, 3H), 3.73 – 3.45 (m, 2H), 3.25 – 3.03 (m, 2H), 2.37 – 2.14 (m, 7H).	B
219		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.32 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 3.99 – 3.79 (m, 6H), 3.64 – 3.45 (m,	C

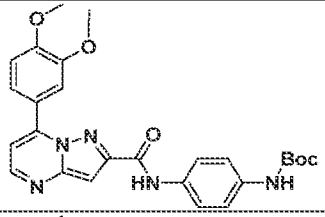
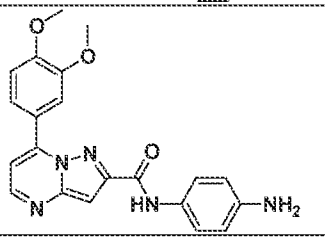
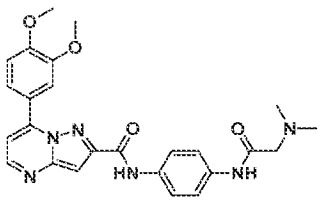
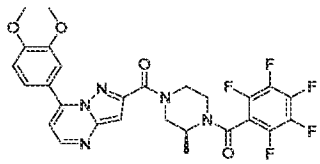
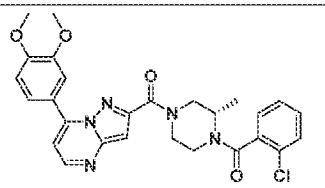
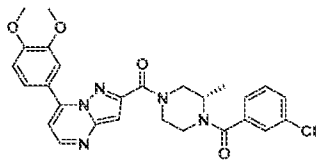
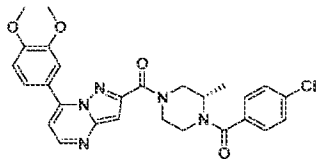
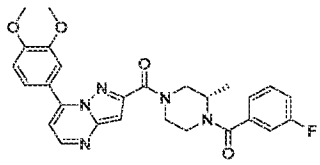
		2H), 2.96 (s, 3H), 2.49 – 2.35 (m, 2H), 2.28 (s, 3H), 2.01 (s, 3H).	
220		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.71 (d, J = 4.1 Hz, 1H), 8.63 – 8.44 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.99 – 7.79 (m, 5H), 7.51 (d, J = 4.3 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.7 Hz, 1H), 4.00 - 3.79 (m, 6H), 2.87 – 2.66 (m, 2H), 2.59 – 2.52 (m, 8H), 1.91 – 1.67 (m, 2H).	C
221		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.77 (s, 1H), 8.78 (s, 1H), 8.71 (d, J = 3.5 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.98 – 7.79 (m, 4H), 7.51 (d, J = 3.5 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.97 - 3.83 (m, 6H), 3.73 – 3.51 (m, 2H), 3.32 – 3.00 (m, 6H), 1.38 – 0.97 (m, 6H).	C
222		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.66 – 8.52 (m, 1H), 8.07 – 7.99 (m, 1H), 7.99 – 7.82 (m, 5H), 7.51 (d, J = 4.4 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.99 – 3.77 (m, 6H), 3.16 – 2.79 (m, 6H), 1.95 – 1.71 (m, 2H), 1.25 – 1.08 (m, 6H).	C
223		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.70 (d, J = 4.3 Hz, 1H), 8.67 – 8.54 (m, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.98 – 7.79 (m, 5H), 7.50 (d, J = 4.2 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.98 - 3.80 (m, 6H), 3.63 – 3.47 (m, 2H), 3.16 – 2.91 (m, 6H), 1.95 – 1.74 (m, 4H).	C
224		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.68 – 8.47 (m, 1H), 8.07 – 8.00 (m, 1H), 8.00 – 7.79 (m, 5H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.05 – 3.74 (m, 6H), 3.45 – 3.38 (m, 2H), 3.30 – 2.89 (m, 6H), 2.06 – 1.74 (m, 6H).	C
225		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.17 – 7.82 (m, 6H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 4.36 (t, J = 5.6 Hz, 2H), 4.01 - 3.79 (m, 6H), 2.90 – 2.70 (m, 2H), 2.62 – 2.52 (m, 4H), 1.79 – 1.56 (m, 4H).	C
226		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.71 (s, 1H), 8.13 – 7.87 (m, 6H), 7.62 – 7.44 (m, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 4.38 – 4.23 (m, 2H), 4.01 - 3.74 (m, 6H), 3.20 – 2.70 (m, 6H), 2.13 – 1.96 (m, 2H), 1.92 – 1.67 (m, 4H).	C

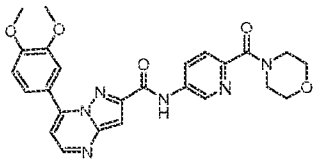
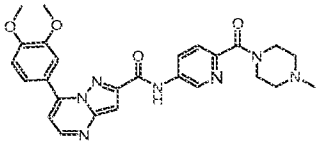
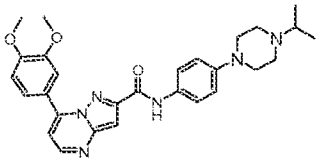
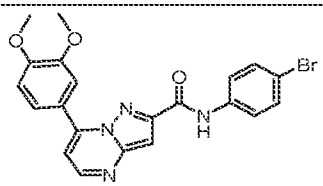
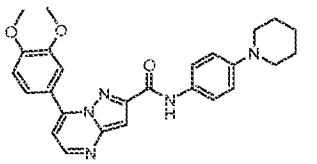
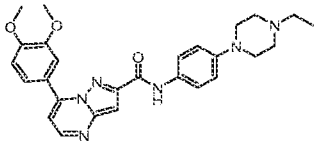
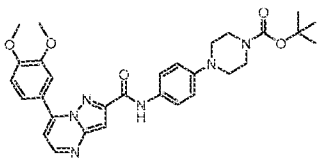
227		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.42 (t, J = 6.1 Hz, 1H), 7.31 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 8.9 Hz, 2H), 3.97 (d, J = 6.1 Hz, 2H), 3.94 – 3.87 (m, 6H), 1.42 (s, 9H).	C
228		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.70 (d, J = 4.3 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.95 (s, 1H), 7.85 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 17.9, 5.6 Hz, 2H), 7.31 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 4.28 – 4.19 (m, 1H), 3.95 – 3.85 (m, 6H), 1.51 – 1.30 (m, 12H).	C
229		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.2 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 9.1 Hz, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.27 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 9.1 Hz, 2H), 3.97 (t, J = 6.5 Hz, 2H), 3.92 – 3.88 (m, 6H), 1.75 – 1.65 (m, 2H), 1.49 – 1.40 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H).	C
230		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.98 - 7.92 (m, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 3.97 – 3.86 (m, 8H), 1.77 – 1.68 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H).	C
231		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 8.76 – 8.62 (m, 1H), 8.39 – 8.17 (m, 1H), 7.96 – 7.71 (m, 4H), 7.45 (d, J = 4.5 Hz, 1H), 7.33 – 7.12 (m, 2H), 4.81 – 4.44 (m, 2H), 3.93 – 3.78 (m, 6H), 3.24 (t, J = 8.4 Hz, 2H).	D
232		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.83 (s, 1H), 8.73 – 8.65 (m, 1H), 7.96 – 7.76 (m, 2H), 7.71 (d, J = 8.2 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.31 – 7.14 (m, 2H), 4.66 (t, J = 8.3 Hz, 2H), 3.90 – 3.84 (m, 6H), 3.26 (t, J = 8.4 Hz, 2H).	D
233		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (dd, J = 14.3, 4.5 Hz, 1H), 7.86 (m, 2H), 7.61 – 7.51 (m, 1H), 7.50 – 7.35 (m, 2H), 7.26 – 6.90 (m, 3H), 4.00 – 3.90 (m, 2H), 3.84 (m, 8H), 2.88 (t, J = 6.6 Hz, 1H), 2.04 – 1.88 (m, 1H).	D

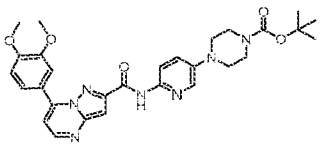
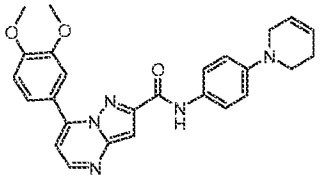
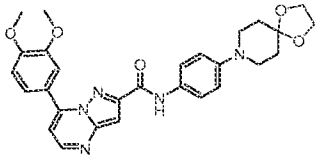
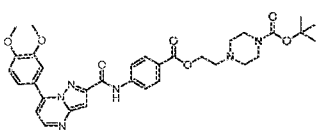
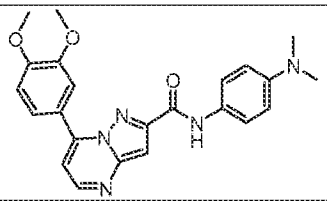
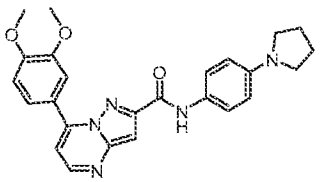
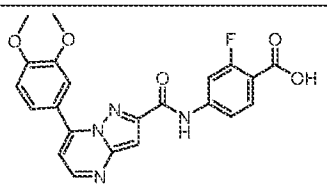
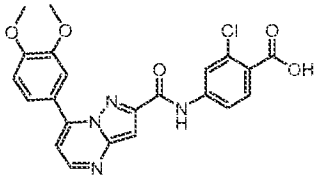
234		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.58 (d, J = 4.5 Hz, 1H), 7.99 – 7.85 (m, 2H), 7.44 (d, J = 1.9 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.03 (d, J = 7.7 Hz, 1H), 6.97 (s, 1H), 6.88 (d, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.48 (s, 3H).	B
235		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.61 – 7.51 (m, 1H), 7.41 (d, J = 4.5 Hz, 1H), 7.30 (s, 1H), 7.23 – 7.08 (m, 2H), 7.08 – 6.97 (m, 2H), 3.94 (t, J = 5.9 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.69 – 3.36 (m, 4H), 2.86 (t, J = 6.5 Hz, 2H), 2.40 – 2.06 (m, 7H), 2.02 – 1.90 (m, 2H).	D
236		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 7.66 (d, J = 1.9 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 4.5 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.26 – 6.99 (m, 4H), 4.01 – 3.91 (m, 2H), 3.91 – 3.83 (m, 3H), 3.80 (s, 3H), 3.71 – 3.38 (m, 8H), 2.86 (t, J = 6.6 Hz, 2H), 2.04 – 1.88 (m, 2H).	D
237		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (dd, J = 4.4, 2.0 Hz, 1H), 7.88 (dd, J = 8.5, 2.1 Hz, 1H), 7.79 (dd, J = 15.8, 2.0 Hz, 1H), 7.41 (d, J = 4.4 Hz, 1H), 7.34 – 7.12 (m, 4H), 7.07 (d, J = 11.9 Hz, 1H), 5.14 (s, 1H), 4.87 (s, 1H), 4.04 (t, J = 5.7 Hz, 1H), 3.96 – 3.78 (m, 7H), 3.69 – 3.51 (m, 2H), 3.49 – 3.36 (m, 2H), 3.01 – 2.87 (m, 2H), 2.43 – 2.10 (m, 7H).	D
238		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, J = 4.4 Hz, 1H), 7.88 (dd, J = 8.5, 2.1 Hz, 1H), 7.79 (dd, J = 15.4, 2.0 Hz, 1H), 7.41 (d, J = 4.4 Hz, 1H), 7.38 – 7.13 (m, 4H), 7.07 (d, J = 10.7 Hz, 1H), 5.14 (s, 1H), 4.88 (s, 1H), 4.04 (t, J = 5.8 Hz, 1H), 3.98 – 3.72 (m, 7H), 3.72 – 3.35 (m, 8H), 3.02 – 2.85 (m, 2H).	D
239		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 9.47 (dd, J = 2.2, 0.8 Hz, 1H), 9.11 (d, J = 2.2 Hz, 1H), 8.08 – 8.02 (m, 2H), 8.02 – 7.97 (m, 2H), 7.50 – 7.41 (m, 2H), 7.33 (d, J = 0.7 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 3.88 – 3.83 (m, 6H).	G
240		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.92 (dd, J = 8.5, 2.2 Hz, 1H), 7.87 (d, J = 7.4 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.16 (s, 1H), 4.10 - 4.02 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.52 – 3.42 (m, 4H), 2.79 – 2.71 (m, 1H), 2.35 – 2.21 (m, 4H), 2.19 (s, 3H), 1.92 – 1.81 (m, 2H), 1.73 – 1.63 (m, 4H), 1.61 – 1.50 (m, 2H).	A

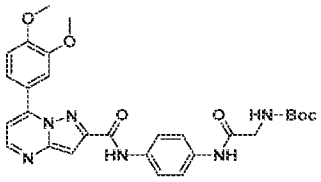
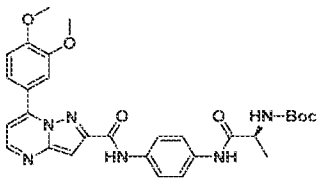
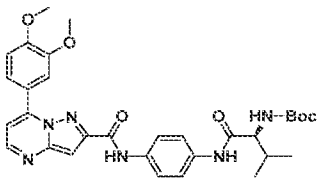
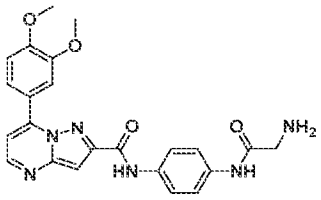
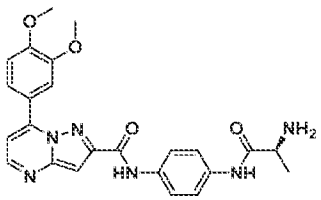
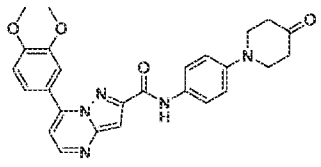
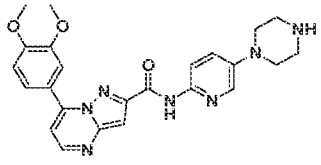
241		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.92 – 3.86 (m, 6H), 3.84 – 3.72 (m, 1H), 3.52 – 3.42 (m, 4H), 2.62 – 2.53 (m, 1H), 2.34 – 2.21 (m, 4H), 2.19 (s, 3H), 1.95 – 1.86 (m, 2H), 1.77 – 1.65 (m, 2H), 1.54 – 1.42 (m, 4H).	A
242		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.93-8.90 (m, 1H), 8.73 (d, J = 4.5 Hz, 1H), 8.41-8.38 (m, 2H), 7.97-7.93 (m, 2H), 7.51 (d, J = 4.5 Hz, 1H), 7.45 (s, 1H), 7.24 (d, J = 8.5 Hz, 1H), 4.42 (t, J = 5.7 Hz, 2H), 3.94-3.88 (m, 6H), 3.57 (t, J = 4.6 Hz, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.49-2.45 (m, 4H).	B
243		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.69 (d, J = 4.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 4.4 Hz, 1H), 7.37 – 7.25 (m, 3H), 7.21 (d, J = 8.5 Hz, 1H), 4.00 – 3.79 (m, 6H), 3.43 (s, 2H), 2.49 – 2.21 (m, 8H), 2.18 (s, 3H).	B
244		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.69 (d, J = 4.4 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.95 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 4.2 Hz, 1H), 7.39 – 7.24 (m, 3H), 7.21 (d, J = 8.6 Hz, 1H), 4.02 – 3.78 (m, 6H), 3.66 – 3.51 (m, 4H), 3.50 – 3.42 (m, 2H), 2.43 – 2.20 (m, 4H).	B
245		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 – 8.76 (m, 1H), 8.64 (d, J = 4.3 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.85 (s, 1H), 7.41 (d, J = 4.2 Hz, 1H), 7.27 – 7.07 (m, 4H), 6.88 (d, J = 8.2 Hz, 2H), 4.40 (d, J = 5.7 Hz, 2H), 3.91 - 3.80 (m, 6H), 3.15 – 2.98 (m, 4H), 2.45 – 2.37 (m, 4H), 2.20 (s, 3H).	B
246		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 – 8.77 (m, 1H), 8.64 (d, J = 4.3 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.85 (s, 1H), 7.41 (d, J = 4.4 Hz, 1H), 7.33 – 7.06 (m, 4H), 6.89 (d, J = 8.4 Hz, 2H), 4.41 (d, J = 5.9 Hz, 2H), 3.89 - 3.82 (m, 6H), 3.80 – 3.67 (m, 4H), 3.17 – 2.98 (m, 4H).	B
247		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.57 – 8.52 (m, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.5, 2.2 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.45 – 7.39 (m, 2H), 7.35 – 7.29 (m, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.14 (s, 1H), 5.20 (s, 2H), 3.99 – 3.91 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.76 – 2.69 (m, 1H), 2.06 – 1.96 (m, 2H), 1.77 – 1.60 (m, 6H).	A

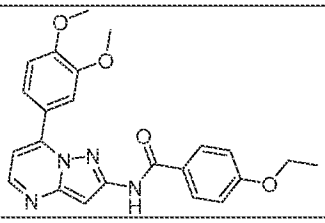
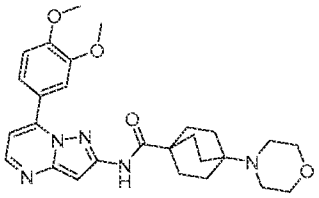
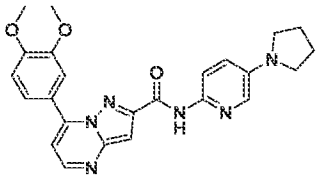
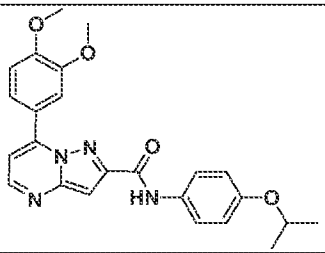
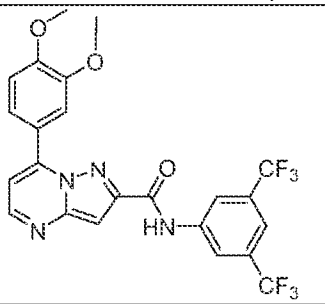
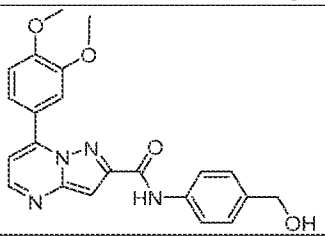
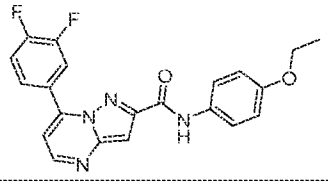
248		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 4.5 Hz, 1H), 7.50 (s, 1H), 7.43 – 7.23 (m, 6H), 7.12 (d, J = 8.7 Hz, 1H), 6.91 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.68 – 3.42 (m, 5H), 3.25 – 3.07 (m, 2H), 2.42 – 1.97 (m, 7H).	B
249		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 4.4 Hz, 1H), 7.50 – 7.27 (m, 7H), 7.12 (d, J = 8.8 Hz, 1H), 6.91 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.75 – 3.34 (m, 9H), 3.30 - 3.00 (m, 2H).	B
250		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 4.5 Hz, 1H), 8.33 – 8.15 (m, 1H), 7.93 – 7.74 (m, 2H), 7.44 (d, J = 4.5 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.32 – 7.14 (m, 3H), 4.73 – 4.55 (m, 2H), 3.95 – 3.77 (m, 6H), 3.62 – 3.36 (m, 4H), 3.23 (t, J = 8.6 Hz, 2H), 2.43 – 2.24 (m, 4H), 2.21 (s, 3H).	D
251		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 4.4 Hz, 1H), 8.33 – 8.19 (m, 1H), 7.96 – 7.70 (m, 2H), 7.44 (d, J = 4.4 Hz, 1H), 7.40 – 7.14 (m, 4H), 4.73 – 4.55 (m, 2H), 4.02 – 3.72 (m, 6H), 3.70 – 3.40 (m, 8H), 3.23 (t, J = 8.6 Hz, 2H).	D
252		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 4.4 Hz, 1H), 8.26 (s, 1H), 7.92 – 7.73 (m, 2H), 7.44 (d, J = 4.4 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.31 – 7.18 (m, 2H), 7.11 (d, J = 8.0 Hz, 1H), 4.73 – 4.53 (m, 2H), 4.01 – 3.74 (m, 6H), 3.72 – 3.35 (m, 4H), 3.26 – 3.18 (m, 2H), 2.44 – 2.26 (m, 4H), 2.22 (s, 3H).	D
253		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 4.5 Hz, 1H), 8.28 (s, 1H), 7.94 – 7.74 (m, 2H), 7.44 (d, J = 4.4 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.31 – 7.17 (m, 2H), 7.14 (d, J = 7.8 Hz, 1H), 4.74 – 4.50 (m, 2H), 3.96 – 3.76 (m, 6H), 3.77 – 3.39 (m, 8H), 3.26 – 3.18 (m, 2H).	D
254		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.45 – 9.42 (m, 1H), 9.08 (d, J = 2.3 Hz, 1H), 7.75 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 2.1 Hz, 1H), 7.43 (dd, J = 8.3, 2.2 Hz, 1H), 7.25 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 9.1 Hz, 2H), 4.03 (q, J = 7.0 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H).	G
255		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 8.5, 2.2 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.20 (d, J = 8.6 Hz, 1H), 7.10 (s, 1H), 4.04 (t, J = 6.4 Hz, 2H), 3.91 – 3.86 (m, 6H), 3.59 – 3.54 (m, 4H), 2.38 – 2.30 (m, 6H), 2.04 – 1.96 (m, 6H), 1.90 – 1.80 (m, 6H), 1.76 – 1.69 (m, 2H).	A

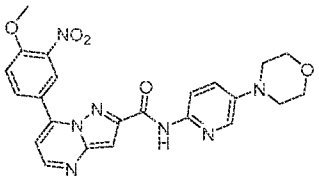
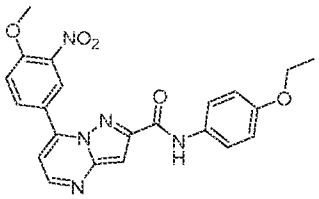
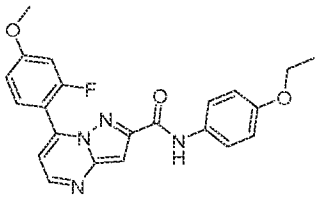
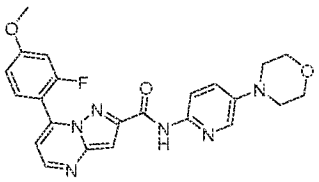
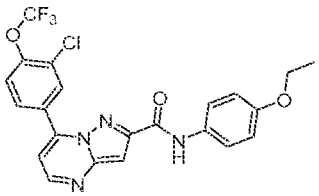
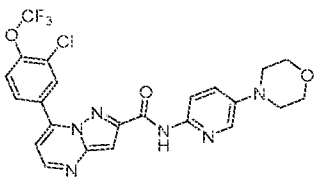
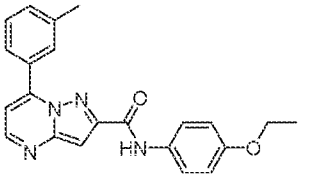
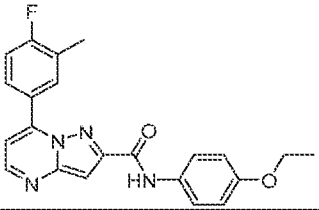
256		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.31 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.0 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 9.0 Hz, 2H), 7.49 – 7.41 (m, 3H), 7.27 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.94 – 3.87 (m, 6H), 1.49 (s, 9H).	C
257		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 8.67 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.46 (d, J = 4.5 Hz, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.24 – 7.19 (m, 2H), 6.57 (d, J = 8.7 Hz, 2H), 4.97 (s, 2H), 3.93 – 3.87 (m, 6H).	C
258		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.75 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.28 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.93 – 3.88 (m, 6H), 3.13 (s, 2H), 2.33 (s, 6H).	C
259		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 - 8.58 (m, 1H), 7.93 – 7.63 (m, 2H), 7.48 – 7.31 (m, 1H), 7.28 – 7.00 (m, 2H), 4.94 – 4.15 (m, 3H), 3.95 – 3.70 (m, 6H), 3.65 – 3.36 (m, 2H), 3.29 – 3.14 (m, 1H), 3.08 – 2.89 (m, 1H), 1.33 – 0.97 (m, 3H).	D
260		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 – 8.57 (m, 1H), 7.92 – 7.65 (m, 2H), 7.62 – 7.29 (m, 5H), 7.27 – 6.97 (m, 2H), 5.00 – 4.16 (m, 3H), 3.99 – 3.67 (m, 6H), 3.61 – 3.36 (m, 1H), 3.28 – 2.91 (m, 3H), 1.37 – 0.89 (m, 3H).	D
261		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 4.3 Hz, 1H), 7.91 – 7.64 (m, 2H), 7.60 – 7.43 (m, 3H), 7.43 – 7.28 (m, 2H), 7.27 – 7.13 (m, 1H), 7.06 (d, J = 22.4 Hz, 1H), 4.67 – 4.15 (m, 3H), 3.97 – 3.69 (m, 6H), 3.59 – 3.36 (m, 1H), 3.30 – 2.90 (m, 3H), 1.37 – 0.99 (m, 3H).	D
262		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.88 – 7.67 (m, 2H), 7.59 – 7.29 (m, 5H), 7.25 – 7.13 (m, 1H), 7.06 (d, J = 23.0 Hz, 1H), 4.66 – 4.15 (m, 3H), 3.95 – 3.67 (m, 6H), 3.58 – 3.40 (m, 1H), 3.28 – 2.89 (m, 3H), 1.28 – 1.00 (m, 3H).	D
263		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 4.2 Hz, 1H), 7.74 (d, J = 24.2 Hz, 2H), 7.51 (dd, J = 13.6, 7.9 Hz, 1H), 7.45 – 7.11 (m, 5H), 7.05 (d, J = 22.9 Hz, 1H), 4.43 (m, 3H), 3.84 (m, 6H), 3.60 – 2.91 (m, 4H), 1.15 (m, 3H).	D

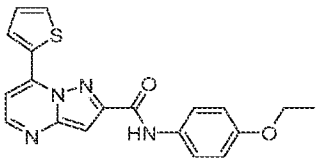
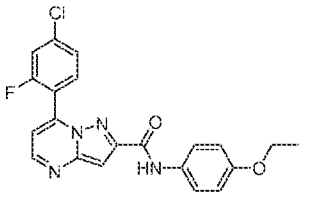
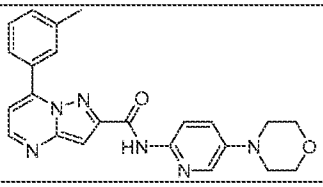
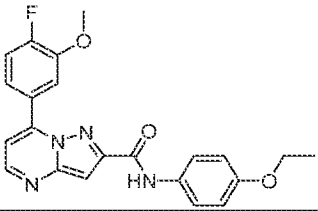
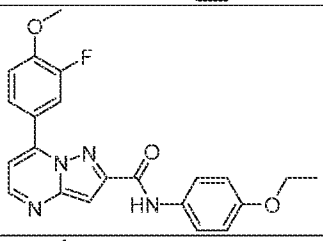
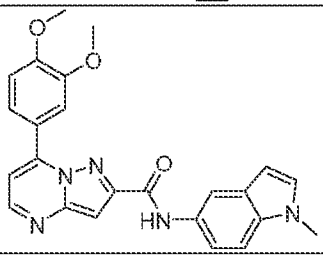
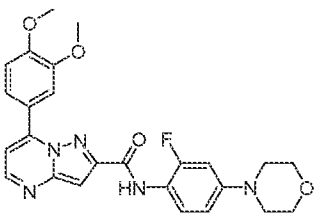
264		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 9.01 (s, 1H), 8.85 – 8.61 (m, 1H), 8.37 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.94 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.58 – 7.42 (m, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.00 - 3.79 (m, 6H), 3.74 – 3.62 (m, 4H), 3.62 – 3.51 (m, 4H).	C
265		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 9.00 (s, 1H), 8.71 (d, J = 3.7 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.50 (d, J = 4.4 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.3 Hz, 1H), 4.00 - 3.72 (m, 6H), 3.73 – 3.56 (m, 2H), 3.55 – 3.42 (m, 2H), 2.43 – 2.34 (m, 2H), 2.34 – 2.24 (m, 2H), 2.20 (s, 3H).	C
266		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.67 (d, J = 4.4 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 4.4 Hz, 1H), 7.25 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 4.06 – 3.72 (m, 6H), 3.22 – 2.99 (m, 4H), 2.84 – 2.54 (m, 5H), 1.18 – 0.86 (m, 6H).	B
268		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.82 (d, J = 8.9 Hz, 2H), 7.57 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.30 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 3.98 – 3.70 (m, 6H).	B
269		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.08 – 7.99 (m, 1H), 7.94 (s, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 4.4 Hz, 1H), 7.25 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 4.00 – 3.79 (m, 6H), 3.19 – 3.01 (m, 4H), 1.73 – 1.57 (m, 4H), 1.57 – 1.44 (m, 2H).	B
270		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.01 (d, J = 7.2 Hz, 1H), 7.95 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 4.2 Hz, 1H), 7.26 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 4.01 – 3.76 (m, 6H), 3.25 – 3.03 (m, 4H), 2.49 – 2.32 (m, 4H), 1.18 - 0.93 (m, 3H).	B
271		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.09 - 7.98 (m, 1H), 7.98 - 7.88 (m, 1H), 7.66 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 4.4 Hz, 1H), 7.26 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 9.0 Hz, 2H), 4.00 – 3.82 (m, 6H), 3.55 – 3.43 (m, 4H), 3.15 – 2.96 (m, 4H), 1.42 (s, 9H).	B

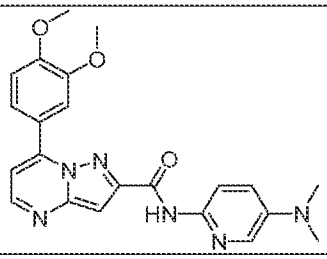
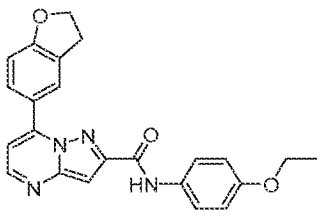
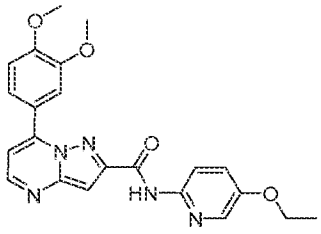
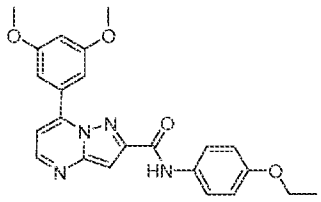
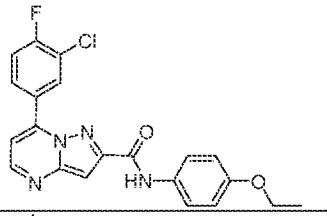
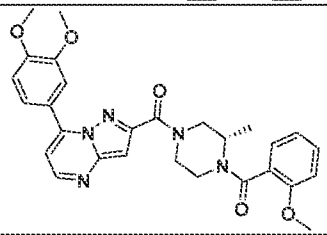
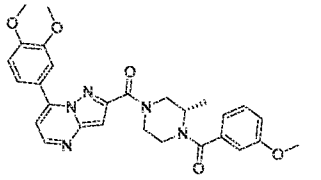
272		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.70 (d, J = 4.2 Hz, 1H), 8.23 – 8.04 (m, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.61 – 7.51 (m, 1H), 7.48 (d, J = 4.4 Hz, 1H), 7.35 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 3.91 (s, 6H), 3.54 – 3.43 (m, 4H), 3.19 – 3.03 (m, 4H), 1.43 (s, 9H).	B
273		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.68 (d, J = 4.3 Hz, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.95 (s, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 3.9 Hz, 1H), 7.26 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 5.96 – 5.69 (m, 2H), 4.01 – 3.79 (m, 6H), 3.74 – 3.55 (m, 2H), 3.33 – 3.29 (m, 2H), 2.31 – 2.14 (m, 2H).	B
274		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.11 – 8.00 (m, 1H), 7.99 - 7.91 (m, 1H), 7.64 (d, J = 8.9 Hz, 2H), 7.48 (d, J = 4.4 Hz, 1H), 7.26 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 9.0 Hz, 2H), 4.07 – 3.73 (m, 10H), 3.31 – 3.16 (m, 4H), 1.86 – 1.65 (m, 4H).	B
275		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.15 – 7.81 (m, 6H), 7.51 (d, J = 4.5 Hz, 1H), 7.35 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.49 – 4.25 (m, 2H), 4.01 – 3.76 (m, 6H), 3.33 – 3.26 (m, 4H), 2.72 (t, J = 5.5 Hz, 2H), 2.49 – 2.39 (m, 4H), 1.40 (s, 9H).	C
276		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.68 (d, J = 4.3 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 4.0 Hz, 1H), 7.25 (s, 1H), 7.22 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 8.3 Hz, 2H), 3.99 – 3.81 (m, 6H), 2.89 (s, 6H).	C
277		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 6.6 Hz, 1H), 7.94 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 4.5 Hz, 1H), 7.33 – 7.10 (m, 2H), 6.55 (d, J = 8.9 Hz, 2H), 3.97 – 3.75 (m, 6H), 3.29 – 3.13 (m, 4H), 2.06 – 1.87 (m, 4H).	B
278		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.70 (d, J = 4.3 Hz, 1H), 8.07 – 7.98 (m, 1H), 7.98 – 7.90 (m, 1H), 7.86 – 7.69 (m, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 4.4 Hz, 1H), 7.32 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 3.99 - 3.78 (m, 6H).	B
279		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.07 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.94 (s, 1H), 7.89 – 7.70 (m, 2H), 7.50 (d, J = 4.4 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.98 - 3.81 (m, 6H).	B

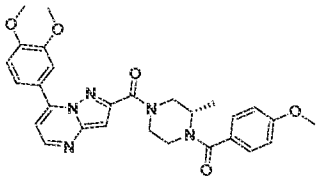
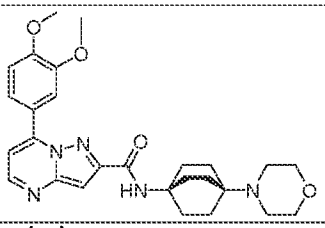
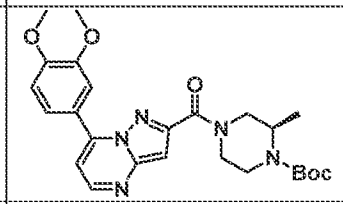
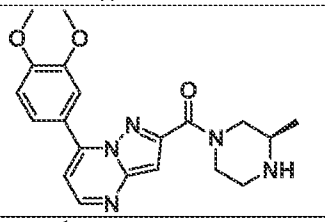
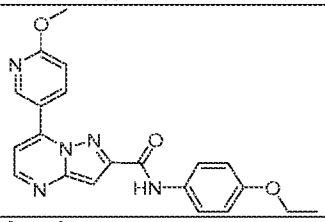
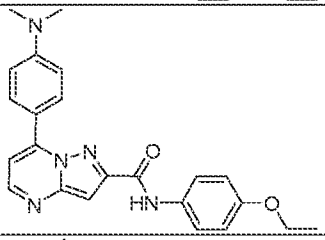
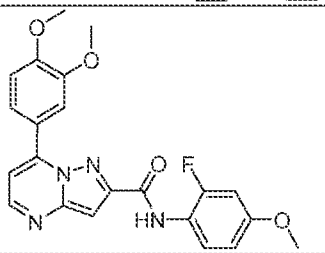
280		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 9.95 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 8.9 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.29 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.07 (t, J = 6.2 Hz, 1H), 3.93 – 3.87 (m, 6H), 3.72 (d, J = 6.1 Hz, 2H), 1.41 (s, 9H).	C
281		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 9.94 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.0 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 8.9 Hz, 2H), 7.60 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.29 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 4.16 – 4.07 (m, 1H), 3.93 – 3.88 (m, 6H), 1.40 (s, 9H), 1.27 (d, J = 7.0 Hz, 3H).	C
282		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.97 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 4.5 Hz, 1H), 7.29 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 3.98 – 3.85 (m, 7H), 2.05 – 1.94 (m, 1H), 1.40 (s, 9H), 0.91 (d, J = 6.6 Hz, 6H).	C
283		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.03 (dd, J = 8.5, 2.1 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 4.4 Hz, 1H), 7.28 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.92 - 3.89 (m, 6H), 3.29 -3.27 (m, 2H).	C
284		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 7.73 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 4.5 Hz, 1H), 7.27 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 3.92 - 3.88 (m, 6H), 3.42 (q, J = 6.9 Hz, 1H), 1.22 (d, J = 6.9 Hz, 3H).	C
285		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.68 (d, J = 4.9 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.96-7.95 (m, 1H), 7.68 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 4.9 Hz, 1H), 7.26 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 9.1 Hz, 2H), 3.92 - 3.88 (m, 6H), 3.59 (t, J = 6.0 Hz, 4H), 2.44 (t, J = 6.0 Hz, 4H).	B
286		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.15-8.12 (m, 2H), 7.96-7.93 (m, 2H), 7.57 (dd, J = 9.0, 3.0 Hz, 1H), 7.48 (d, J = 4.5 Hz, 1H), 7.36 (s, 1H), 7.24 (d, J = 8.2 Hz, 1H), 3.94 - 3.89 (m, 6H), 3.38-3.36 (m, 4H), 3.24-3.22 (m, 4H).	B

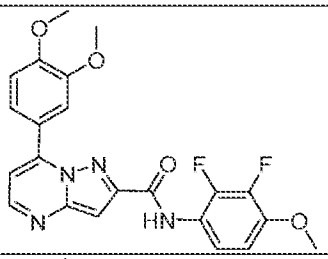
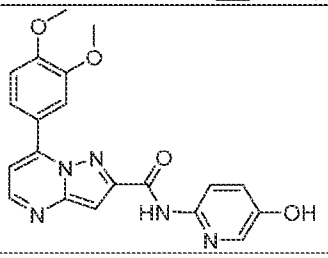
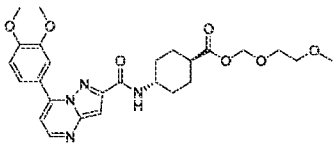
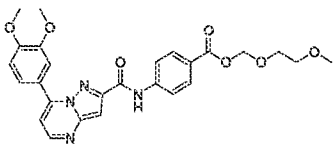
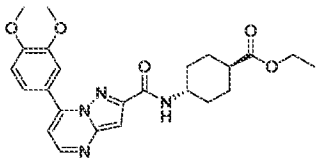
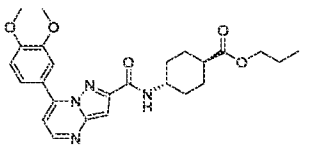
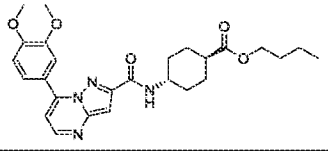
287		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 8.51 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 8.9 Hz, 2H), 7.84 - 7.78 (m, 2H), 7.20 - 7.15 (m, 2H), 7.13 (s, 1H), 7.03 (d, J = 9.0 Hz, 2H), 4.12 (q, J= 7.0 Hz, 2H), 3.90 - 3.84 (m, 6H), 1.35 (t, J = 7.0 Hz, 3H).	F
288		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.47 (d, J = 4.5 Hz, 1H), 7.80 (dd, J = 8.5, 2.1 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.17 -7.13 (m, 2H), 6.96 (s, 1H), 3.88 - 3.84 (m, 6H), 3.55 - 3.49 (m, 4H), 2.47 - 2.41 (m, 4H), 1.90 - 1.82 (m, 6H), 1.56 - 1.47 (m, 6H).	F
289		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 8.9 Hz, 1H), 7.96 (dd, J = 8.5 Hz, 2.1 Hz, 1H), 7.90 (d, J = 4.9 Hz, 1H), 7.72 (d, J = 2.9 Hz, 1H), 7.48 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.08 (dd, J = 9.0, 3.0 Hz, 1H), 3.94-3.89 (m, 6H), 3.31-3.25 (m, 4H), 1.99-1.96 (m, 4H).	B
290		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 7.68 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 4.5 Hz, 1H), 7.26 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 4.63 - 4.53 (m, 1H), 3.92 - 3.86 (m, 6H), 1.28 - 1.24 (m, 6H).	C
291		1H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.60 (s, 2H), 8.01 (dd, J = 8.5, 2.2 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.85 (s, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.92 - 3.88 (m, 6H).	B
292		1H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7. 76 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.34 - 7.28 (m, 3H), 7.21 (d, J = 8.6 Hz, 1H), 5.17 (t, J = 5.7 Hz, 1H), 4.47 (d, J = 5.7 Hz, 2H), 3.92 - 3.86 (m, 6H).	C
293		1H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.74 (d, J = 4.4 Hz, 1H), 8.52 - 8.45 (m, 1H), 8.22 - 8.15 (m, 1H), 7.77 - 7.65 (m, 3H), 7.49 (d, J = 4.4 Hz, 1H), 7.32 (s, 1H), 6.97 - 6.91 (m, 2H), 4.01 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H).	B

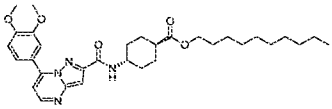
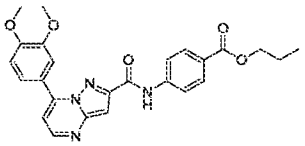
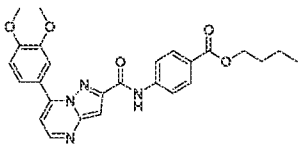
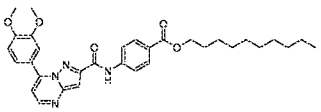
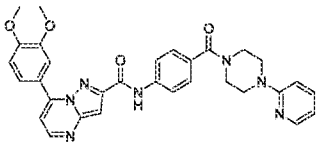
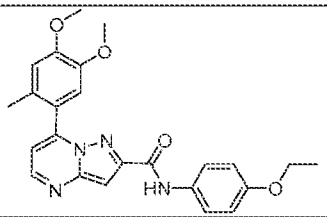
294		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.86 (d, J = 2.3 Hz, 1H), 8.74 (d, J = 4.4 Hz, 1H), 8.61 (dd, J = 8.9, 2.3 Hz, 1H), 8.12 - 8.06 (m, 2H), 7.63 (d, J = 9.0 Hz, 1H), 7.54 - 7.48 (m, 2H), 7.39 (s, 1H), 4.10 (s, 3H), 3.80 - 3.70 (m, 4H), 3.20 - 3.10 (m, 4H).	B
295		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.94 (d, J = 2.3 Hz, 1H), 8.73 (d, J = 4.4 Hz, 1H), 8.65 (dd, J = 8.9, 2.3 Hz, 1H), 7.71 - 7.66 (m, 2H), 7.61 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 4.4 Hz, 1H), 7.31 (s, 1H), 6.98 - 6.91 (m, 2H), 4.10 - 3.98 (m, 5H), 1.33 (t, J = 7.0 Hz, 3H).	C
296		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.70 (d, J = 4.3 Hz, 1H), 7.94 (t, J = 8.6 Hz, 1H), 7.68 - 7.62 (m, 2H), 7.33 - 7.29 (m, 2H), 7.13 (dd, J = 12.5, 2.4 Hz, 1H), 7.03 (dd, J = 8.7, 2.5 Hz), 6.93 - 6.87 (m, 2H), 4.01 (q, J = 7.0 Hz, 2H), 3.90 (s, 3H), 1.32 (t, J = 7.0 Hz, 2H).	C
297		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.72 (d, J = 4.3 Hz, 1H), 8.10 - 8.04 (m, 2H), 7.93 (t, J = 8.6 Hz, 1H), 7.50 (dd, J = 9.1, 3.1 Hz, 1H), 7.40 (s, 1H), 7.33 (dd, J = 4.3, 0.8 Hz, 1H), 7.17 (dd, J = 12.5, 2.4 Hz, 1H), 7.06 (dd, J = 8.7, 2.5 Hz, 1H), 3.91 (s, 3H), 3.78 -3.71 (m, 4H), 3.17 - 3.11 (m, 4H).	B
298		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.76 (d, J = 4.4 Hz, 1H), 8.57 (d, J = 2.2 Hz, 1H), 8.41 (dd, J = 8.7, 2.2 Hz, 1H), 7.87 - 7.81 (m, 1H), 7.71 - 7.64 (m, 2H), 7.54 (d, J = 4.4 Hz, 1H), 7.34 (s, 1H), 6.96 - 6.90 (m, 2H), 4.01 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H).	C
299		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.77 (d, J = 4.4 Hz, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.37 (dd, J = 8.7. 2,2 Hz, 1H), 8.12 - 8.05 (m, 2H), 7.90 - 7.84 (m, 1H), 7.56 - 7.48 (m, 2H), 7.43 (s, 1H), 3.80 - 3.70 (m, 4H), 3.18 - 3.12 (m, 4H).	B
301		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.09-8.04 (m, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.56-7.47 (m, 2H), 7.40 (d, J = 4.4 Hz, 1H), 7.30 (s, 1H), 6.94 (d, J = 9.0 Hz, 2H), 4.02 (q, J = 7.0 Hz, 2H), 2.46 (s, 1H), 1.33 (t, J = 7.0 Hz, 3H).	B
302		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.24-8.20 (m, 2H), 7.70-7.68 (m, 2H), 7.44-7.40 (m, 2H), 7.30 (s, 1H), 6.95-6.93 (m, 2H), 4.02 (q, J = 7.0 Hz, 2H), 2.40-2.38 (m, 3H), 1.33 (t, J = 7.0 Hz, 3H).	C

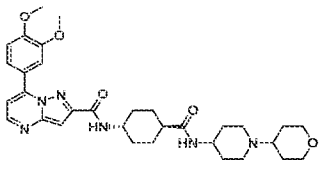
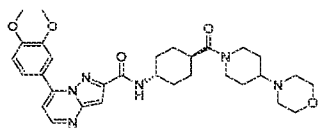
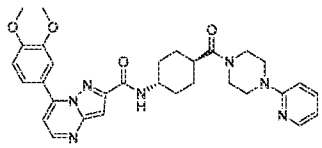
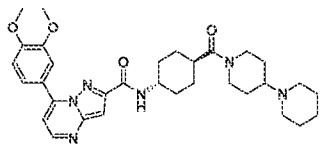
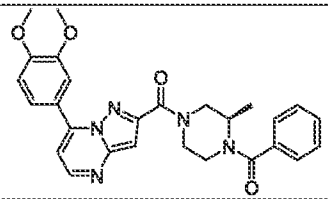
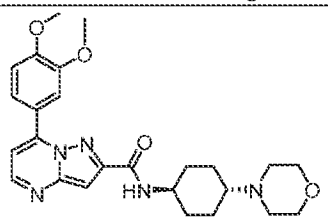
303		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.75 (dd, J = 3.9, 1.1 Hz, 1H), 8.70 (d, J = 4.7 Hz, 1H), 8.16 (dd, J = 5.0, 1.1 Hz, 1H), 7.84 (d, J = 4.7 Hz, 1H), 7.74-7.72 (m, 2H), 7.45-7.43 (m, 1H), 7.32 (s, 1H), 6.98-6.96 (m, 2H), 4.04 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H).	C
304		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.76 (d, J = 4.2 Hz, 1H), 8.01 (t, J = 8.0 Hz, 1H), 7.79 (dd, J = 10.1, 1.9 Hz, 1H), 7.65 (d, J = 9.0 Hz, 2H), 7.59 (dd, J = 8.4, 1.9 Hz, 1H), 7.39 (d, J = 4.2 Hz, 1H), 7.36 (s, 1H), 6.92 (d, J = 9.0 Hz, 2H), 4.01 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H).	C
306		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.73 (d, J = 4.4 Hz, 1H), 8.11-8.05 (m, 3H), 7.97 (s, 1H), 7.58-7.48 (m, 3H), 7.40-7.39 (m, 2H), 3.76 (t, J = 4.8 Hz, 4H), 3.15 (t, J = 4.8 Hz, 4H), 2.46 (s, 3H).	B
307		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.73 (d, J = 4.4 Hz, 1H), 8.09 (dd, J = 8.4, 2.1 Hz, 1H), 7.94-7.90 (m, 1H), 7.70-7.68 (m, 2H), 7.52-7.47 (m, 2H), 7.31 (s, 1H), 6.95-6.93 (m, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.99 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H).	C
308		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.32 (dd, J = 12.9, 2.2 Hz, 1H), 8.25-8.23 (m, 1H), 7.70-7.68 (m, 2H), 7.47 (d, J = 4.5 Hz, 1H), 7.42 (t, J = 8.9 Hz, 1H), 7.28 (s, 1H), 6.95-6.93 (m, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.98 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H).	C
309		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.07-8.04 (m, 2H), 7.96 (d, J = 2.1 Hz, 1H), 7.49-7.48 (m, 2H), 7.44-7.42 (m, 1H), 7.34 (d, J = 3.2 Hz, 1H), 7.29 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 6.43 (dd, J = 3.0, 0.7 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H).	C
311		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 7.97-7.93 (m, 2H), 7.64 (t, J = 9.0 Hz, 1H), 7.48 (d, J = 4.5 Hz, 1H), 7.26 (s, 1H), 7.20 (d, J = 8.5 Hz, 1H), 6.92 (dd, J = 14.1, 2.6 Hz, 1H), 6.81 (dd, J = 8.9, 2.4 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.74 (t, J = 4.8 Hz, 4H), 3.15 (t, J = 4.8 Hz, 4H).	B

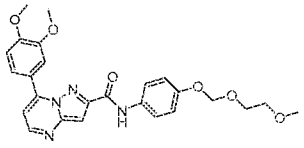
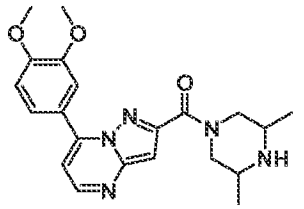
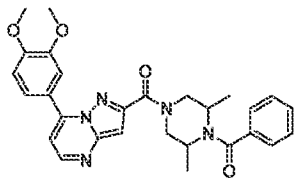
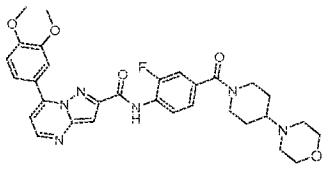
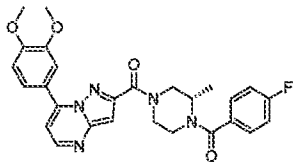
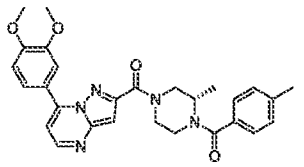
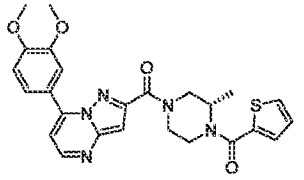
312		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.95 (dd, J = 8.5, 2.1 Hz, 1H), 7.91-7.89 (m, 2H), 7.47 (d, J = 4.5 Hz, 1H), 7.33 (s, 1H), 7.29 (dd, J = 9.1, 3.1 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 3.92-3.90 (m, 6H), 2.92 (s, 6H).	B
313		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 8.27 (s, 1H), 8.11 (dd, J = 8.5, 2.0 Hz, 1H), 7.71-7.69 (m, 2H), 7.35 (d, J = 4.8 Hz, 1H), 7.25 (s, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.95-6.92 (m, 2H), 4.68 (t, J = 8.8 Hz, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.39-3.34 (m, 2H), 1.33 (t, J = 7.0 Hz, 3H).	C
314		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.16 (d, J = 9.1 Hz, 1H), 8.09 (d, J = 2.9 Hz, 1H), 7.96 (dd, J = 8.5, 2.1 Hz, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.48 (d, J = 4.5 Hz, 1H), 7.36 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.93 - 3.87 (m, 6H), 1.35 (t, J = 7.0 Hz, 3H).	B
315		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 7.67 (d, J = 9.1 Hz, 2H), 7.45 (d, J = 4.4 Hz, 1H), 7.38 (d, J = 2.3 Hz, 2H), 7.30 (s, 1H), 6.95 - 6.90 (m, 2H), 6.78 (t, J = 2.3 Hz, 1H), 4.01 (q, J = 7.0 Hz, 2H), 3.90 - 3.82 (m, 6H), 1.32 (t, J = 7.0 Hz, 3H).	C
316		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.74 (d, J = 4.4 Hz, 1H), 8.51 (dd, J = 7.2, 2.3 Hz, 1H), 8.39 - 8.31 (m, 1H), 7.74 - 7.64 (m, 3H), 7.49 (d, J = 4.4 Hz, 1H), 7.32 (s, 1H), 6.98 - 6.89 (m, 2H), 4.01 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H).	C
317		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 - 8.52 (m, 1H), 7.80 - 7.53 (m, 2H), 7.44 - 7.28 (m, 1H), 7.25 - 6.83 (m, 6H), 5.23 - 4.36 (m, 3H), 4.05 - 3.74 (m, 10H), 3.70 - 2.77 (m, 3H), 1.39 - 1.07 (m, 3H).	D
318		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 - 8.53 (m, 1H), 7.76 - 7.54 (m, 2H), 7.38 - 7.30 (m, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.08 - 6.89 (m, 5H), 4.95 - 4.47 (m, 3H), 4.04 - 3.78 (m, 10H), 3.63 - 2.69 (m, 3H), 1.41 - 1.19 (m, 3H).	D

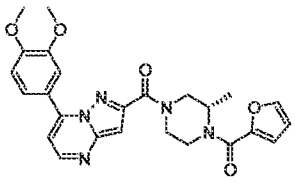
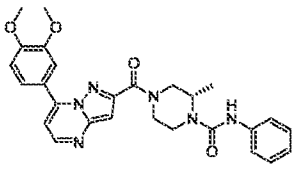
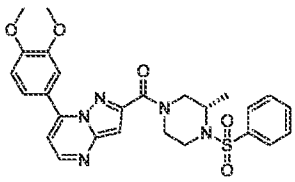
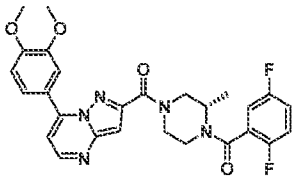
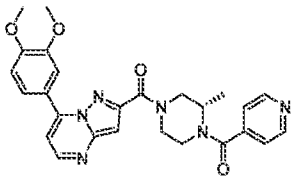
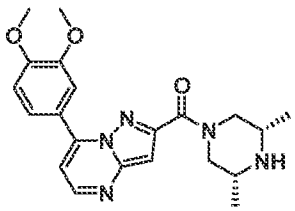
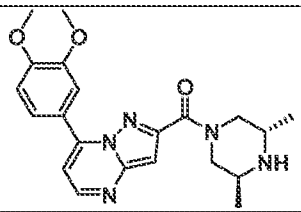
319		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 - 8.54 (m, 1H), 7.75 - 7.54 (m, 2H), 7.41 - 7.32 (m, 2H), 7.17 (d, J = 7.3 Hz, 1H), 7.07 - 6.90 (m, 4H) , 4.86 - 4.42 (m, 3H), 4.03 - 3.79 (m, 10H), 3.46 - 2.86 (m, 3H), 1.38 - 1.19 (m, 3H).	D
320		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.4 Hz, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 8.4, 2.1 Hz, 1H), 7.25 (s, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 4.4 Hz, 1H), 6.82 (s, 1H), 4.01 (s, 3H), 3.97 (s, 3H), 3.75 - 3.68 (m, 4H), 2.60 - 2.51 (m, 4H), 2.12 - 2.06 (m, 6H), 1.78 - 1.69 (m, 6H).	A
321		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 - 8.53 (m, 1H), 7.74 - 7.58 (m, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.07 - 6.95 (m, 2H), 4.70 - 4.18 (m, 3H), 4.03 - 3.80 (m, 7H), 3.43 - 2.87 (m, 3H), 1.51 - 1.41 (m, 9H), 1.24 - 1.08 (m, 3H).	D
322		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 - 8.52 (m, 1H), 7.76 - 7.65 (m, 2H), 7.12 - 7.07 (m, 1H), 7.06 - 6.95 (m, 2H), 4.71 - 4.43 (m, 2H), 4.01 - 3.87 (m, 6H), 3.26 - 3.07 (m, 1H), 3.01 - 2.45 (m, 4H), 1.18 - 0.95 (m, 3H).	D
323		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.18 (d, J = 2.3 Hz, 1H), 8.74 - 8.63 (m, 2H), 7.71 - 7.64 (m, 2H), 7.50 (d, J = 4.4 Hz, 1H), 7.28 (s, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.97 - 6.90 (m, 2H), 4.06 - 3.98 (m, 5H), 1.33 (t, J = 7.0 Hz, 3H).	C
324		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.59 (d, J = 4.6 Hz, 1H), 8.37 (d, J = 9.1 Hz, 2H), 7.74 - 7.67 (m, 2H), 7.37 (d, J = 4.6 Hz, 1H), 7.19 (s, 1H), 6.98 - 6.86 (m, 4H), 4.02 (q, J = 7.0 Hz, 2H), 3.07 (s, 6H), 1.33 (t, J = 7.0 Hz, 3H).	C
325		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.10 - 7.87 (m, 2H), 7.67 (t, J = 9.0 Hz, 1H), 7.48 (d, J = 4.5 Hz, 1H), 7.27 (s, 1H), 7.20 (d, J = 8.6 Hz, 1H), 6.98 (dd, J = 12.4, 2.7 Hz, 1H), 6.90 - 6.80 (m, 1H), 3.95 - 3.86 (m, 6H), 3.79 (s, 3H).	C

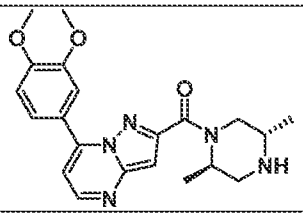
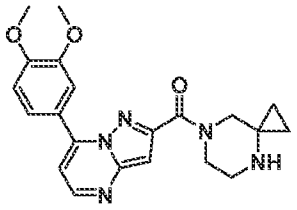
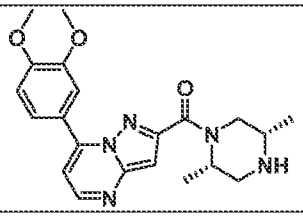
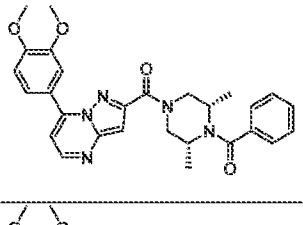
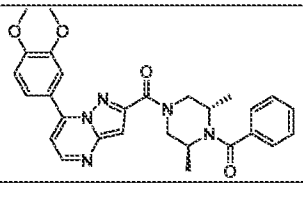
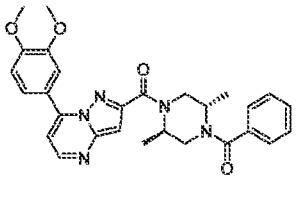
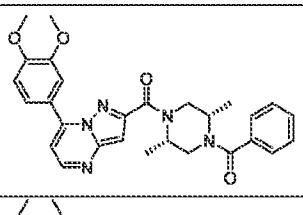
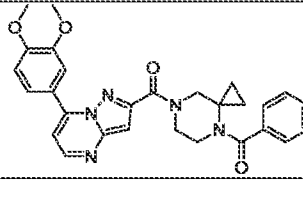
326		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.58 - 7.38 (m, 2H), 7.28 (s, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.07 (t, J = 8.4 Hz, 1H), 3.94 - 3.85 (m, 9H).	C
327		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 - 9.67 (m, 2H), 8.70 (d, J = 4.5 Hz, 1H), 8.07 (d, J = 8.9 Hz, 1H), 7.99 - 7.85 (m, 3H), 7.48 (d, J = 4.5 Hz, 1H), 7.38 - 7.27 (m, 2H), 7.23 (d, J = 8.6 Hz, 1H), 3.91 (s, 6H).	B
328		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 4.0 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.13 (s, 1H), 5.25 (s, 2H), 3.89 (s, 6H), 3.85 - 3.75 (m, 1H), 3.75 - 3.65 (m, 2H), 3.53 - 3.43 (m, 2H), 3.25 (s, 3H), 2.39 - 2.20 (m, 1H), 2.07 - 1.82 (m, 4H), 1.58 - 1.37 (m, 4H).	A
329		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.10 - 7.98 (m, 5H), 7.96 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 5.50 (s, 2H), 3.97 - 3.86 (m, 6H), 3.86 - 3.78 (m, 2H), 3.55 - 3.45 (m, 2H), 3.24 (s, 3H).	C
330		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.90 (dd, J = 8.5, 2.0 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.95 - 3.85 (m, 6H), 3.84 - 3.73 (m, 1H), 2.31 - 2.18 (m, 1H), 2.02 - 1.81 (m, 4H), 1.53 - 1.36 (m, 4H), 1.19 (t, J = 7.1 Hz, 3H).	A
331		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 3.98 (t, J = 6.6 Hz, 2H), 3.94 - 3.86 (m, 6H), 3.85 - 3.70 (m, 1H), 2.35 - 2.20 (m, 1H), 2.06 - 1.81 (m, 4H), 1.68 - 1.52 (m, 2H), 1.52 - 1.35 (m, 4H), 0.89 (t, J = 7.4 Hz, 3H).	A
332		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.5, 2.0 Hz, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 4.02 (t, J = 6.5 Hz,	A

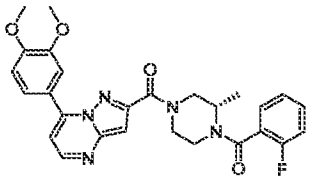
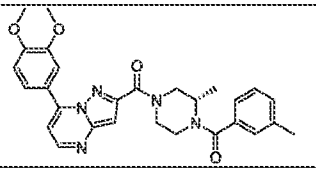
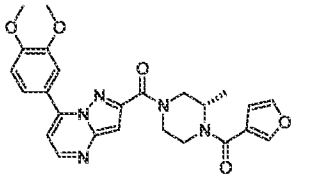
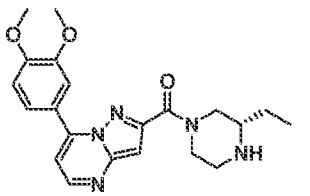
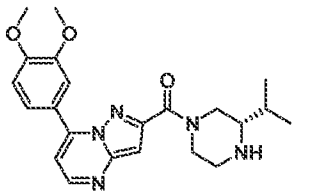
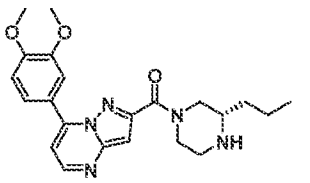
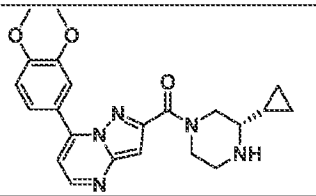
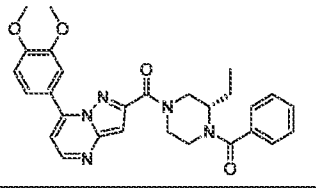
		2H), 3.95 - 3.84 (m, 6H), 3.83 - 3.72 (m, 1H), 2.33 - 2.19 (m, 1H), 2.05 - 1.80 (m, 4H), 1.63 - 1.51 (m, 2H), 1.51 - 1.38 (m, 4H), 1.38 - 1.27 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).	
333		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 4.01 (t, J = 6.5 Hz, 2H), 3.94 - 3.85 (m, 6H), 3.83 - 3.72 (m, 1H), 2.33 - 2.20 (m, 1H), 2.03 - 1.81 (m, 4H), 1.62 - 1.51 (m, 2H), 1.51 - 1.36 (m, 4H), 1.33 - 1.18 (m, 14H), 0.86 (t, J = 6.8 Hz, 3H).	A
335		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.07 - 7.91 (m, 6H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.22 (t, J = 6.6 Hz, 2H), 3.94 - 3.85 (m, 6H), 1.79 - 1.67 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H).	C
336		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 8.08 - 7.91 (m, 6H), 7.51 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.27 (t, J = 6.5 Hz, 2H), 3.98 - 3.85 (m, 6H), 1.78 - 1.63 (m, 2H), 1.51 - 1.37 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H).	C
337		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.09 - 7.91 (m, 6H), 7.51 (d, J = 4.5 Hz, 1H), 7.35 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.26 (t, J = 6.5 Hz, 2H), 3.97 - 3.80 (m, 6H), 1.77 - 1.65 (m, 2H), 1.49 - 1.13 (m, 14H), 0.94 - 0.79 (m, 3H).	C
338		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.13 (dd, J = 4.8, 1.4 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.99 - 7.88 (m, 3H), 7.61 - 7.53 (m, 1H), 7.53 - 7.45 (m, 3H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.71 - 6.65 (m, 1H), 3.96 - 3.85 (m, 6H), 3.81 - 3.43 (m, 8H).	C
339		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.70 (d, J = 4.2 Hz, 1H), 7.68 - 7.58 (m, 2H), 7.32 (s, 1H), 7.20 - 7.12 (m, 2H), 7.04 (s, 1H), 6.94 - 6.86 (m, 2H), 4.00 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 2.08 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H).	C

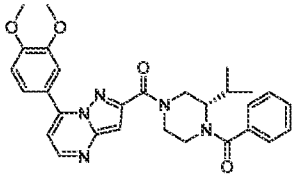
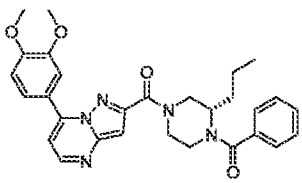
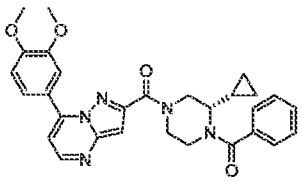
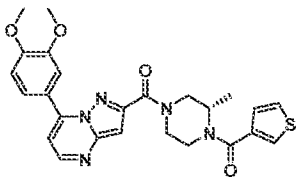
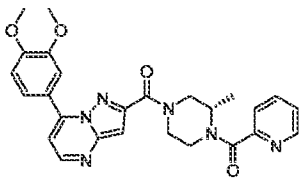
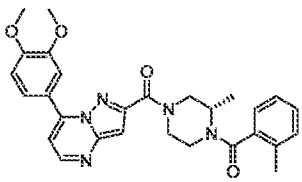
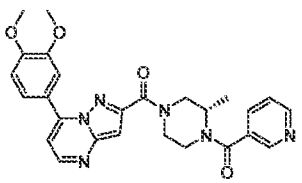
340		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 1.7 Hz, 1H), 7.88 (dd, J = 8.5, 1.6 Hz, 1H), 7.75 - 7.62 (m, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 0.5 Hz, 1H), 3.96 - 3.83 (m, 8H), 3.82 - 3.71 (m, 1H), 3.59 - 3.48 (m, 1H), 3.31 - 3.20 (m, 3H), 3.03 - 2.81 (m, 2H), 2.43 - 2.17 (m, 2H), 2.13 - 1.98 (m, 1H), 1.95 - 1.83 (m, 2H), 1.81 - 1.62 (m, 6H), 1.57 - 1.28 (m, 8H).	A
341		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 4.5 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 4.44 - 4.32 (m, 1H), 3.98 - 3.91 (m, 1H), 3.91 - 3.84 (m, 6H), 3.83 - 3.71 (m, 1H), 3.56 (t, J = 4.2 Hz, 4H), 3.06 - 2.95 (m, 1H), 2.48 - 2.41 (m, 4H), 2.41 - 2.30 (m, 1H), 1.95 - 1.66 (m, 6H), 1.54 - 1.39 (m, 4H), 1.36 - 1.07 (m, 4H).	A
342		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 4.5 Hz, 1H), 8.19 - 8.08 (m, 2H), 7.97 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 8.5, 2.1 Hz, 1H), 7.61 - 7.51 (m, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.14 (s, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.71 - 6.63 (m, 1H), 3.96 - 3.84 (m, 6H), 3.85 - 3.73 (m, 1H), 3.66 - 3.41 (m, 8H), 2.66 - 2.55 (m, 1H), 1.98 - 1.84 (m, 2H), 1.83 - 1.69 (m, 2H), 1.59 - 1.38 (m, 4H).	A
343		^{1}H NMR (400 MHz, MeOD-d_4) δ 8.61 (d, J = 4.5 Hz, 1H), 7.88 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 8.5, 2.1 Hz, 1H), 7.28 (d, J = 4.5 Hz, 1H), 7.24 - 7.15 (m, 2H), 4.70 - 4.60 (m, 1H), 4.22 - 4.09 (m, 1H), 4.00 - 3.95 (m, 6H), 3.18 - 3.06 (m, 1H), 2.82 - 2.52 (m, 7H), 2.16 - 1.93 (m, 4H), 1.91 - 1.79 (m, 2H), 1.75 - 1.60 (m, 6H), 1.59 - 1.35 (m, 7H).	A
344		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.75 - 7.54 (m, 2H), 7.49 - 7.33 (m, 5H), 7.17 (d, J = 7.4 Hz, 1H), 7.07 - 6.94 (m, 2H), 5.04 - 4.44 (m, 3H), 4.07 - 3.85 (m, 7H), 3.51 - 2.85 (m, 3H), 1.37 - 1.22 (m, 3H).	D
345		^{1}H NMR (400 MHz, MeOD-d_4) δ 8.59 (d, J = 4.5 Hz, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 8.5, 2.1 Hz, 1H), 7.27 (d, J = 4.5 Hz, 1H), 7.21 - 7.14 (m, 2H), 3.98 - 3.85 (m, 7H), 3.78 - 3.67 (m, 4H), 2.77 - 2.63 (m, 4H), 2.51 - 2.36 (m, 1H), 2.18 - 2.01 (m, 4H), 1.55 - 1.38 (m, 4H).	A

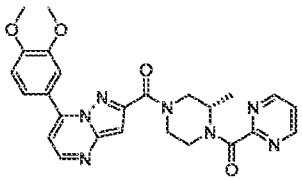
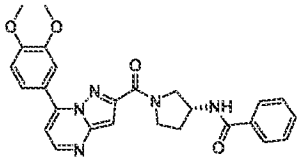
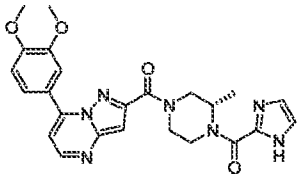
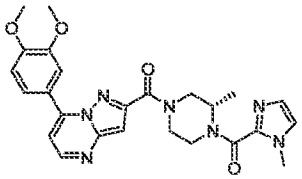
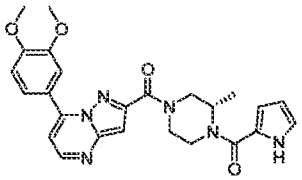
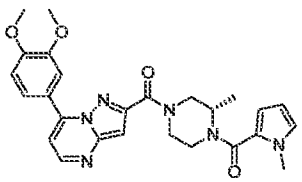
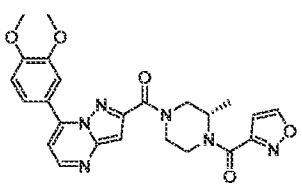
346		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.64 (d, J = 4.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.70 - 7.63 (m, 2H), 7.43 (d, J = 4.5 Hz, 1H), 7.23 (s, 1H), 7.16 (d, J = 8.6 Hz, 1H), 7.03 - 6.96 (m, 2H), 5.19 (s, 2H), 3.90 - 3.81 (m, 6H), 3.73 - 3.63 (m, 2H), 3.45 - 3.39 (m, 2H), 3.18 (s, 3H).	C
347		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.4 Hz, 1H), 7.72 (dd, J = 8.4, 2.1 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H), 7.09 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 4.4 Hz, 1H), 4.74 - 4.65 (m, 1H), 4.54 - 4.46 (m, 1H), 4.00 - 3.94 (m, 6H), 3.00 - 2.85 (m, 2H), 2.77 - 2.67 (m, 1H), 2.46 - 2.37 (m, 1H), 1.15 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H).	D
348		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.4 Hz, 1H), 7.66 (dd, J = 8.4, 1.6 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.45 - 7.39 (m, 3H), 7.38 - 7.32 (m, 2H), 7.21 (s, 1H), 7.06 - 6.94 (m, 2H), 4.86 - 4.22 (4H), 4.02 - 3.90 (m, 6H) 3.45 -3.30 (m, 1H), 3.09 - 2.96 (m, 1H), 1.44 - 1.33 (m, 3H), 1.32 - 1.24 (m, 3H).	D
349		^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, J = 3.1 Hz, 1H), 8.65 - 8.60 (m, 2H), 7.85 (d, J = 2.1 Hz, 1H), 7.63 (dd, J = 8.4, 2.1 Hz, 1H), 7.43 (s, 1H), 7.28 - 7.22 (m, 2H), 7.10 (dd, J = 6.4, 2.1 Hz, 2H), 4.80 - 4.50 (m, 1H), 4.06 - 3.96 (m, 6H), 3.95 - 3.79 (m, 1H), 3.78 - 3.66 (m, 4H), 3.16 - 2.70 (m, 2H), 2.64 - 2.52 (m, 4H), 2.51 - 2.38 (m, 1H), 2.06 - 1.74 (m, 2H), 1.56 - 1.35 (m, 2H).	B
350		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (dd, J = 4.3, 1.8 Hz, 1H), 7.83 - 7.70 (m, 2H), 7.53 - 7.46 (m, 2H), 7.38 (dd, J = 9.1, 4.3 Hz, 1H), 7.34 - 7.26 (m, 2H), 7.21 - 7.14 (m, 1H), 7.05 (d, J = 23.7 Hz, 1H), 4.77 - 4.24 (m, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.56 - 3.47 (m, 1H), 3.27 - 2.95 (m, 3H), 1.23 - 1.06 (m, 3H).	D
351		^{1}H NMR (400 MHz, DMSO-d6) δ 8.66 (dd, J = 4.2, 2.3 Hz, 1H), 7.86 - 7.69 (m, 2H), 7.38 (dd, J = 9.6, 4.3 Hz, 1H), 7.34 - 7.24 (m, 4H), 7.22 - 7.13 (m, 1H), 7.06 (d, J = 24.2 Hz, 1H), 4.62 - 4.25 (m, 3H), 3.94 - 3.72 (m, 6H), 3.51 - 3.47 (m, 1H), 3.29 - 2.93 (m, 3H), 2.35 (s, 3H), 1.27 - 1.01 (m, 3H).	D
352		^{1}H NMR (400 MHz, DMSO-d6) δ 8.70 - 8.63 (m, 1H), 7.85 - 7.72 (m, 3H), 7.46 - 7.35 (m, 2H), 7.23 - 7.12 (m, 2H), 7.07 (d, J = 23.6 Hz, 1H), 4.75 - 4.03 (m, 5H), 3.94 - 3.80 (m, 6H), 3.53 (dd, J = 13.5, 3.4 Hz, 1H), 3.20 - 3.00 (m, 1H), 1.31 - 1.12 (m, 3H).	D

353		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (dd, J = 4.3, 1.6 Hz, 1H), 7.89 - 7.70 (m, 3H), 7.39 (dd, J = 8.8, 4.4 Hz, 1H), 7.20 (dd, J = 8.4, 3.9 Hz, 1H), 7.11 - 7.01 (m, 2H), 6.67 - 6.61 (m, 1H), 4.78 - 4.10 (m, 5H), 3.90 - 3.81 (m, 6H), 3.57 - 3.48 (m, 1H), 3.20 - 2.99 (m, 1H), 1.30 - 1.12 (m, 3H).	D
354		^{1}H NMR (400 MHz, DMSO-d6) δ 8.71 - 8.63 (m, 1H), 8.55 (d, J = 3.8 Hz, 1H), 7.89 - 7.70 (m, 2H), 7.52 - 7.35 (m, 3H), 7.30 - 7.16 (m, 3H), 7.14 - 7.02 (m, 1H), 6.94 (t, J = 7.3 Hz, 1H), 4.59 - 4.27 (m, 3H), 4.06 - 3.97 (m, 1H), 3.95 - 3.82 (m, 6H), 3.52 - 3.40 (m, 1H), 3.32 - 2.93 (m, 2H), 1.20 - 1.02 (m, 3H).	D
355		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (t, J = 4.3 Hz, 1H), 7.89 - 7.73 (m, 4H), 7.73 - 7.58 (m, 3H), 7.38 (dd, J = 10.9, 4.4 Hz, 1H), 7.19 (dd, J = 12.3, 8.6 Hz, 1H), 7.01 (d, J = 26.4 Hz, 1H), 4.46 - 3.97 (m, 3H), 3.95 - 3.77 (m, 6H), 3.77 - 3.58 (m, 1H), 3.31 - 3.07 (m, 2H), 2.99 - 2.77 (m, 1H), 0.99 - 0.82 (m, 3H).	D
356		^{1}H NMR (400 MHz, DMSO-d6) δ 8.73 - 8.62 (m, 1H), 7.90 - 7.66 (m, 2H), 7.49 - 7.28 (m, 4H), 7.26 - 7.00 (m, 2H), 4.94 - 4.19 (m, 3H), 3.97 - 3.71 (m, 6H), 3.71 - 3.48 (m, 1H), 3.30 - 2.90 (m, 3H), 1.32 - 1.02 (m, 3H).	D
357		^{1}H NMR (400 MHz, DMSO-d6) δ 8.76 - 8.59 (m, 3H), 7.90 - 7.64 (m, 2H), 7.50 - 7.30 (m, 3H), 7.26 - 6.98 (m, 2H), 4.93 - 4.15 (m, 4H), 3.95 - 3.68 (m, 6H), 3.65 - 3.46 (m, 1H), 3.19 - 2.91 (m, 2H), 1.33 - 1.00 (m, 3H).	D
358		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 4.4 Hz, 1H), 7.84 - 7.74 (m, 2H), 7.37 (d, J = 4.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.01 (s, 1H), 4.54 - 4.31 (m, 2H), 3.91 - 3.82 (m, 6H), 2.89 - 2.61 (m, 3H), 2.36 (t, J = 12.2 Hz, 1H), 1.06 (d, J = 6.1 Hz, 3H), 0.91 (d, J = 6.0 Hz, 3H).	D
359		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 4.5 Hz, 1H), 7.84 - 7.73 (m, 2H), 7.37 (d, J = 4.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.00 (s, 1H), 3.97 - 3.65 (m, 8H), 3.53 - 3.42 (m, 2H), 3.22 - 3.05 (m, 2H), 1.06 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H).	D

360		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 4.4 Hz, 1H), 7.91 - 7.70 (m, 2H), 7.37 (d, J = 4.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 4.73 - 3.97 (m, 2H), 3.94 - 3.75 (m, 6H), 3.29 - 3.01 (m, 4H), 1.30 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H).	D
361		^{1}H NMR (400 MHz, DMSO-d6) δ 8.64 (dd, J = 6.3, 4.5 Hz, 1H), 7.85 - 7.64 (m, 2H), 7.36 (dd, J = 18.4, 4.4 Hz, 1H), 7.19 (dd, J = 12.2, 8.6 Hz, 1H), 6.99 (d, J = 18.0 Hz, 1H), 3.92 - 3.82 (m, 6H), 3.80 - 3.50 (m, 4H), 2.84 - 2.73 (m, 2H), 0.56 - 0.45 (m, 2H), 0.42 - 0.34 (m, 2H).	D
362		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 4.4 Hz, 1H), 7.90 - 7.70 (m, 2H), 7.37 (t, J = 4.6 Hz, 1H), 7.18 (dd, J = 8.4, 5.9 Hz, 1H), 6.99 (s, 1H), 4.72 - 4.14 (m, 2H), 3.92 - 3.82 (m, 6H), 2.93 - 2.53 (m, 4H), 1.37 - 1.20 (m, 3H), 1.13 - 0.88 (m, 3H).	D
363		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (d, J = 4.4 Hz, 1H), 7.83 - 7.74 (m, 1H), 7.71 (s, 1H), 7.52 - 7.42 (m, 3H), 7.42 - 7.32 (m, 3H), 7.17 (d, J = 8.6 Hz, 1H), 7.08 (s, 1H), 4.59 - 4.21 (m, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.52 - 3.40 (m, 2H), 3.18 - 3.07 (m, 1H), 1.34 - 1.04 (m, 6H).	D
364		^{1}H NMR (400 MHz, DMSO-d6) δ 8.74 - 8.57 (m, 1H), 7.97 - 7.70 (m, 2H), 7.57 - 7.27 (m, 6H), 7.20 (d, J = 7.3 Hz, 1H), 7.15 - 7.02 (m, 1H), 4.48 - 3.98 (m, 4H), 3.96 - 3.63 (m, 8H), 1.35 - 1.00 (m, 6H).	D
365		^{1}H NMR (400 MHz, DMSO-d6) δ 8.71 - 8.60 (m, 1H), 7.87 (dd, J = 34.8, 7.5 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.54 - 7.28 (m, 6H), 7.26 - 7.10 (m, 1H), 7.04 (dd, J = 24.4, 8.8 Hz, 1H), 5.00 - 4.49 (m, 1H), 4.38 - 4.08 (m, 2H), 4.00 - 3.68 (m, 6H), 3.63 - 3.43 (m, 1H), 3.32 - 3.11 (m, 2H), 1.35 - 1.06 (m, 6H).	D
366		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (d, J = 4.4 Hz, 1H), 7.88 - 7.57 (m, 2H), 7.53 - 7.19 (m, 6H), 7.19 - 7.00 (m, 2H), 4.83 - 4.57 (m, 1H), 4.55 - 4.06 (m, 3H), 3.94 - 3.74 (m, 6H), 3.31 - 2.84 (m, 2H), 1.23 - 0.93 (m, 6H).	D
367		^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 - 8.62 (m, 1H), 7.95 - 7.64 (m, 2H), 7.53 - 7.29 (m, 6H), 7.23 - 7.11 (m, 1H), 7.09 - 7.00 (m, 1H), 4.07 - 3.53 (m, 12H), 1.02 - 0.42 (m, 4H).	D

368		^{1}H NMR (400 MHz, DMSO-d6) δ 8.72 - 8.60 (m, 1H), 7.89 - 7.66 (m, 2H), 7.59 - 7.16 (m, 6H), 7.15 - 6.99 (m, 1H), 4.95 - 4.54 (m, 1H), 4.53 - 4.23 (m, 2H), 3.96 - 3.69 (m, 6H), 3.65 - 3.48 (m, 1H), 3.30 - 2.87 (m, 3H), 1.31 - 0.98 (m, 3H).	D
369		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 3.3 Hz, 1H), 7.90 - 7.67 (m, 2H), 7.46 - 7.00 (m, 7H), 4.72 - 4.21 (m, 3H), 3.94 - 3.69 (m, 6H), 3.56 - 3.42 (m, 1H), 3.32 - 2.91 (m, 3H), 2.33 (s, 3H), 1.33 - 0.98 (m, 3H).	D
370		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (dd, J = 4.3, 1.9 Hz, 1H), 8.05 (d, J = 2.9 Hz, 1H), 7.87 - 7.69 (m, 3H), 7.39 (dd, J = 9.4, 4.4 Hz, 1H), 7.19 (dd, J = 8.6, 3.7 Hz, 1H), 7.07 (d, J = 22.3 Hz, 1H), 6.69 (s, 1H), 4.62 - 3.96 (m, 3H), 3.94 - 3.80 (m, 6H), 3.48 (dd, J = 13.3, 3.1 Hz, 1H), 3.32 - 2.93 (m, 3H), 1.28 - 1.08 (m, 3H).	D
371		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 4.4 Hz, 1H), 7.86 - 7.72 (m, 2H), 7.39 (d, J = 4.4 Hz, 1H), 7.19 (dd, J = 11. 5 , 8.5 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 4.47 - 4.22 (m, 2H), 3.93 - 3.81 (m, 6H), 3.21 - 2.96 (m, 2H), 2.94 - 2.58 (m, 3H), 1.46 - 1.18 (m, 2H), 0.97 - 0.66 (m, 3H).	D
372		^{1}H NMR (400 MHz, DMSO-d6) δ 8.68 - 8.62 (m, 1H), 7.86 - 7.71 (m, 2H), 7.38 (d, J = 4.5 Hz, 1H), 7.19 (t, J = 8.9 Hz, 1H), 7.00 (d, J = 4.5 Hz, 1H), 4.49 - 4.18 (m, 2H), 3.92 - 3.82 (m, 6H), 3.16 - 2.97 (m, 1H), 2.91 - 2.54 (m, 3H), 2.37 - 2.24 (m, 1H), 1.68 - 1.35 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.78 - 0.56 (m, 3H).	D
373		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (dd, J = 4.4, 1.6 Hz, 1H), 7.85 - 7.71 (m, 2H), 7.37 (t, J = 4.6 Hz, 1H), 7.18 (dd, J = 11.9, 8.6 Hz, 1H), 7.00 (d, J = 3.1 Hz, 1H), 4.43 - 4.19 (m, 2H), 3.91 - 3.81 (m, 6H), 3.16 - 2.57 (m, 5H), 1.45 - 1.29 (m, 2H), 1.24 - 0.99 (m, 2H), 0.95 - 0.66 (m, 3H).	D
374		^{1}H NMR (400 MHz, DMSO-d6) d 8.65 (t, J = 4.3 Hz, 1H), 7.85 - 7.71 (m, 2H), 7.38 (dd, J = 4.4, 1.4 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 4.49 - 4.23 (m, 2H), 3.90 - 3.81 (m, 6H), 3.21 - 2.53 (m, 5H), 1.96 - 1.85 (m, 1H), 0.84 - -0.31 (m, 4H).	D
375		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 3.1 Hz, 1H), 7.91 - 7.64 (m, 2H), 7.45 - 7.30 (m, 6H), 7.29 - 6.98 (m, 2H), 4.80 - 4.21 (m, 3H), 3.99 - 3.63 (m, 6H), 3.61 - 3.42 (m, 1H), 3.31 - 2.85 (m, 3H), 1.80 - 1.39 (m, 2H), 0.83 - 0.33 (m, 3H).	D

376		^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (dd, J = 12.3, 3.9 Hz, 1H), 7.88 - 7.66 (m, 2H), 7.53 - 7.33 (m, 6H), 7.28 - 7.03 (m, 2H), 4.82 - 4.15 (m, 3H), 3.95 - 3.71 (m, 6H), 3.67 - 3.42 (m, 1H), 3.29 - 2.84 (m, 3H), 2.11 - 1.90 (m, 1H), 1.16 - 0.45 (m, 6H).	D
377		^{1}H NMR (400 MHz, DMSO-d6) δ 8.66 (d, J = 3.4 Hz, 1H), 7.91 - 7.61 (m, 2H), 7.53 - 7.29 (m, 6H), 7.26 - 7.11 (m, 1H), 7.11 - 7.00 (m, 1H), 4.88 - 4.16 (m, 3H), 3.97 - 3.66 (m, 6H), 3.59 - 3.40 (m, 1H), 3.29 - 2.83 (m, 3H), 1.80 - 0.38 (m, 7H).	D
378		^{1}H NMR (400 MHz, DMSO-d6) δ 8.66 (d, J = 4.4 Hz, 1H), 7.88 - 7.68 (m, 2H), 7.51 - 7.33 (m, 6H), 7.23 - 7.13 (m, 1H), 7.06 (d, J = 19.0 Hz, 1H), 4.74 - 4.37 (m, 3H), 3.93 - 3.71 (m, 6H), 3.62 - 3.38 (m, 2H), 3.25 - 3.11 (m, 1H), 3.10 - 2.97 (m, 1H), 1.39 - 1.21 (m, 1H), 0.59 - 0.02 (m, 4H).	D
379		^{1}H NMR (400 MHz, DMSO-d6) δ 8.66 (dd, J = 4.3, 2.3 Hz, 1H), 7.86 - 7.70 (m, 3H), 7.67 - 7.61 (m, 1H), 7.38 (dd, J = 9.5, 4.4 Hz, 1H), 7.26 - 7.14 (m, 2H), 7.07 (d, J = 23.3 Hz, 1H), 4.62 - 4.27 (m, 3H), 3.92 - 3.76 (m, 6H), 3.54 - 3.44 (m, 1H), 3.32 - 3.08 (m, 2H), 3.06 - 2.93 (m, 1H), 1.25 - 1.06 (m, 3H).	D
380		^{1}H NMR (400 MHz, DMSO-d6) δ 8.72 - 8.54 (m, 2H), 8.01 - 7.90 (m, 1H), 7.88 - 7.66 (m, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.54 - 7.44 (m, 1H), 7.44 - 7.32 (m, 1H), 7.27 - 7.00 (m, 2H), 4.94 - 4.55 (m, 1H), 4.51 - 4.26 (m, 2H), 4.15 - 3.37 (m, 8H), 3.31 - 2.92 (m, 2H), 1.32 - 1.06 (m, 3H).	D
381		^{1}H NMR (400 MHz, DMSO-d6) δ 8.66 (dd, J = 11.8, 3.9 Hz, 1H), 7.90 - 7.76 (m, 1H), 7.76 - 7.63 (m, 1H), 7.44 - 7.14 (m, 5H), 7.09 (d, J = 7.4 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 4.98 - 4.19 (m, 3H), 3.93 - 3.67 (m, 6H), 3.66 - 3.44 (m, 1H), 3.28 - 2.81 (m, 3H), 2.32 - 2.09 (m, 3H), 1.31 - 0.95 (m, 3H).	D
382		^{1}H NMR (400 MHz, DMSO-d6) δ 8.74 - 8.59 (m, 3H), 7.93 - 7.65 (m, 3H), 7.56 - 7.44 (m, 1H), 7.43 - 7.32 (m, 1H), 7.27 - 7.12 (m, 1H), 7.06 (d, J = 23.5 Hz, 1H), 4.95 - 4.16 (m, 3H), 3.99 - 3.66 (m, 6H), 3.60 - 3.40 (m, 1H), 3.31 - 2.93 (m, 3H), 1.34 - 1.02 (m, 3H).	D

383		^{1}H NMR (400 MHz, DMSO-d6) δ 8.96 - 8.86 (m, 2H), 8.71 - 8.61 (m, 1H), 7.89 - 7.66 (m, 2H), 7.66 - 7.56 (m, 1H), 7.44 - 7.32 (m, 1H), 7.27 - 7.00 (m, 2H), 4.92 - 4.56 (m, 1H), 4.50 - 4.23 (m, 2H), 3.95 - 3.72 (m, 6H), 3.71 - 3.55 (m, 1H), 3.28 - 2.93 (m, 3H), 1.32 - 1.06 (m, 3H).	D
384		^{1}H NMR (400 MHz, DMSO-d6) δ 8.71 - 8.61 (m, 2H), 7.90 - 7.74 (m, 4H), 7.57 - 7.50 (m, 1H), 7.50 - 7.36 (m, 3H), 7.23 - 7.09 (m, 2H), 4.64 - 4.48 (m, 1H), 4.35 - 4.26 (m, 1H), 4.19 - 4.04 (m, 1H), 3.99 - 3.82 (m, 4H), 3.82 - 3.73 (m, 3H), 3.71 - 3.58 (m, 1H), 2.30 - 1.96 (m, 2H).	D
385		^{1}H NMR (400 MHz, DMSO-d6) δ 12.95 (s, 1H), 8.67 (d, J = 4.1 Hz, 1H), 7.88 - 7.70 (m, 2H), 7.43 - 7.34 (m, 1H), 7.27 (s, 1H), 7.24 - 7.16 (m, 1H), 7.14 - 7.02 (m, 2H), 6.23 - 5.63 (m, 1H), 4.94 - 4.51 (m, 2H), 4.51 - 4.23 (m, 2H), 3.92 - 3.80 (m, 6H), 3.66 - 3.48 (m, 1H), 3.25 - 3.07 (m, 1H), 1.36 - 1.07 (m, 3H).	D
386		^{1}H NMR (400 MHz, DMSO-d6) δ 8.66 (d, J = 4.0 Hz, 1H), 7.91 - 7.69 (m, 2H), 7.46 - 7.27 (m, 2H), 7.26 - 7.13 (m, 1H), 7.12 - 6.94 (m, 2H), 5.08 - 4.27 (m, 4H), 3.94 - 3.73 (m, 9H), 3.21 - 3.04 (m, 3H), 1.34 - 1.10 (m, 3H).	D
387		^{1}H NMR (400 MHz, DMSO-d6) δ 11.49 (s, 1H), 8.67 (dd, J = 4.3, 2.0 Hz, 1H), 7.89 - 7.69 (m, 2H), 7.39 (dd, J = 9.0, 4.4 Hz, 1H), 7.20 (dd, J = 8.6, 3.3 Hz, 1H), 7.07 (d, J = 24.1 Hz, 1H), 6.91 (s, 1H), 6.56 - 6.45 (m, 1H), 6.14 (s, 1H), 4.91 - 4.18 (m, 5H), 3.98 - 3.78 (m, 6H), 3.58 - 3.47 (m, 1H), 3.19 - 2.99 (m, 1H), 1.34 - 1.10 (m, 3H).	D
388		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (dd, J = 4.4, 2.3 Hz, 1H), 7.87 - 7.69 (m, 2H), 7.38 (dd, J = 9.4, 4.5 Hz, 1H), 7.19 (dd, J = 8.5, 3.9 Hz, 1H), 7.06 (d, J = 22.5 Hz, 1H), 6.94 - 6.88 (m, 1H), 6.36 - 6.30 (m, 1H), 6.07 - 6.01 (m, 1H), 4.78 - 4.04 (m, 5H), 3.91 - 3.81 (m, 6H), 3.66 (d, J = 1.9 Hz, 3H), 3.52 - 3.42 (m, 1H), 3.17 - 2.94 (m, 1H), 1.27 - 1.09 (m, 3H).	D
389		^{1}H NMR (400 MHz, DMSO-d6) δ 9.17 - 9.07 (m, 1H), 8.73 - 8.63 (m, 1H), 7.88 - 7.67 (m, 2H), 7.44 - 7.33 (m, 1H), 7.26 - 7.01 (m, 2H), 6.91 - 6.83 (m, 1H), 4.92 - 4.07 (m, 5H), 3.92 - 3.76 (m, 6H), 3.64 - 3.43 (m, 1H), 3.27 - 2.93 (m, 1H), 1.28 - 1.12 (m, 3H).	D

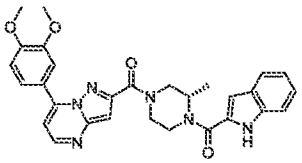
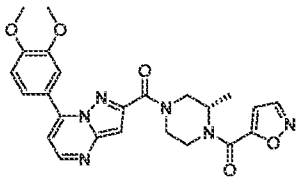
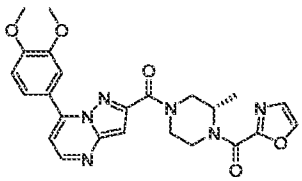
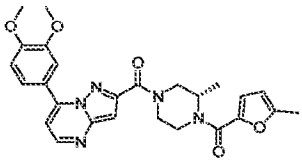
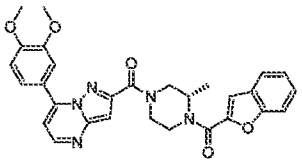
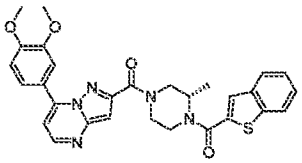
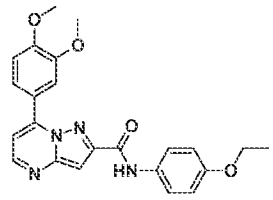
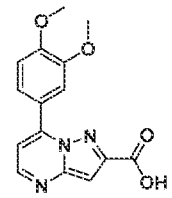
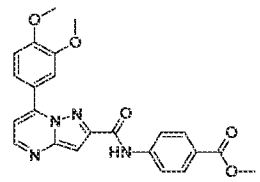
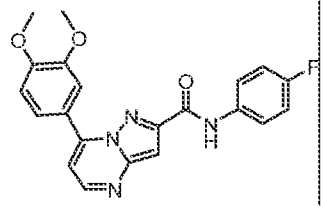
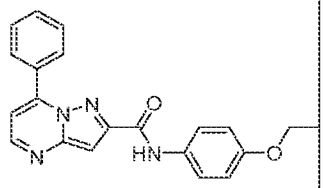
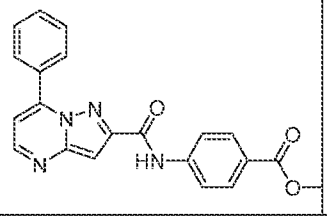
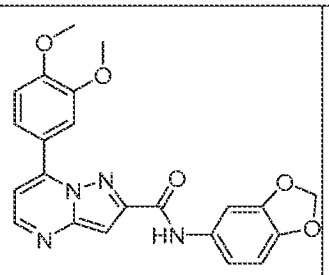
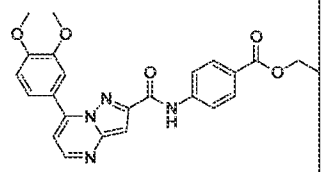
390		^{1}H NMR (400 MHz, DMSO-d6) δ 11.65 - 11.59 (m, 1H), 8.67 (dd, J = 4.4, 2.5 Hz, 1H), 7.87 - 7.71 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.24 - 7.16 (m, 2H), 7.14 - 7.02 (m, 2H), 6.82 (d, J = 8.0 Hz, 1H), 4.94 - 4.25 (m, 5H), 3.92 - 3.81 (m, 6H), 3.57 (dd, J = 13.6, 3.6 Hz, 1H), 3.24 - 3.05 (m, 1H), 1.35 - 1.16 (m, 3H).	D
391		^{1}H NMR (400 MHz, DMSO-d6) δ 8.76 (s, 1H), 8.67 (d, J = 4.3 Hz, 1H), 7.89 - 7.67 (m, 2H), 7.39 (dd, J = 9.4, 4.4 Hz, 1H), 7.26 - 7.13 (m, 1H), 7.08 (d, J = 24.6 Hz, 1H), 6.96 (s, 1H), 4.91 - 3.97 (m, 4H), 3.93 - 3.74 (m, 6H), 3.64 - 3.45 (m, 1H), 3.25 - 2.93 (m, 2H), 1.36 - 1.09 (m, 3H).	D
392		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (dd, J = 4.3, 1.8 Hz, 1H), 8.61 (s, 1H), 8.56 - 8.51 (m, 1H), 7.85 - 7.71 (m, 2H), 7.38 (dd, J = 9.4, 4.5 Hz, 1H), 7.23 - 7.16 (m, 1H), 7.07 (d, J = 24.2 Hz, 1H), 4.96 - 4.23 (m, 5H), 3.91 - 3.80 (m, 6H), 3.60 - 3.44 (m, 1H), 3.22 - 2.91 (m, 1H), 1.28 - 1.09 (m, 3H).	D
393		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (dd, J = 4.4, 1.6 Hz, 1H), 7.86 - 7.71 (m, 2H), 7.39 (dd, J = 8.6, 4.5 Hz, 1H), 7.20 (dd, J = 8.5, 3.6 Hz, 1H), 7.07 (d, J = 22.7 Hz, 1H), 6.90 (t, J = 3.9 Hz, 1H), 6.26 (d, J = 3.3 Hz, 1H), 4.80 - 4.10 (m, 5H), 3.91 - 3.81 (m, 6H), 3.52 (dd, J = 14.3, 3.9 Hz, 1H), 3.20 - 2.98 (m, 1H), 2.32 (s, 3H), 1.30 - 1.11 (m, 3H).	D
394		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (dd, J = 4.3, 1.7 Hz, 1H), 7.86 - 7.71 (m, 3H), 7.70 - 7.63 (m, 1H), 7.50 - 7.31 (m, 4H), 7.19 (dd, J = 8.3, 3.4 Hz, 1H), 7.09 (d, J = 23.8 Hz, 1H), 4.84 - 4.13 (m, 5H), 3.91 - 3.78 (m, 6H), 3.63 - 3.52 (m, 1H), 3.24 - 3.02 (m, 1H), 1.36 - 1.14 (m, 3H).	D
395		^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 (dd, J = 4.3, 2.8 Hz, 1H), 8.07 - 8.00 (m, 1H), 7.97 - 7.90 (m, 1H), 7.86 - 7.70 (m, 3H), 7.51 - 7.42 (m, 2H), 7.39 (dd, J = 10.0, 4.5 Hz, 1H), 7.19 (dd, J = 8.4, 5.1 Hz, 1H), 7.08 (d, J = 23.0 Hz, 1H), 4.79 - 4.09 (m, 5H), 3.88 - 3.79 (m, 6H), 3.58 (dd, J = 13.3, 3.0 Hz, 1H), 3.24 - 3.03 (m, 1H), 1.33 - 1.14 (m, 3H).	D

Table 3B – Compound Structures, Characterization Data and Synthetic Method

Cmpd	Structure	Characterization Data	General Method (Example 2)
3		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.58 (d, J = 4.3 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.62 – 7.57 (m, 2H), 7.40 (s, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 4.4 Hz, 1H), 6.93 – 6.88 (m, 2H), 4.09 – 3.95 (m, 8H), 1.42 (t, J = 7.0 Hz, 3H).	C
5		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.35 (s, 1H), 8.67 (d, J = 4.4 Hz, 1H), 7.90 (dd, J = 8.5, 2.1 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.44 (d, J = 4.4 Hz, 1H), 7.25 – 7.15 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H).	A (Example 1)
11		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.05 – 7.94 (m, 6H), 7.51 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 3.93 – 3.89 (m, 6H), 3.85 (s, 3H).	C
267		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 1.9 Hz, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 9.0, 5.0 Hz, 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.29 (s, 1H), 7.26 – 7.12 (m, 3H), 3.96 – 3.81 (m, 6H).	B
300		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.73 (d, J = 4.4 Hz, 1H), 8.28-8.26 (m, 2H), 7.69-7.65 (m, 5H), 7.43 (d, J = 4.4 Hz, 1H), 7.31 (s, 1H), 6.95-6.92 (m, 2H), 4.02 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H).	C
305		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.75 (d, J = 4.4 Hz, 1H), 8.29-8.26 (m, 2H), 8.00-7.98 (m, 4H), 7.68-7.66 (m, 3H), 7.45 (d, J = 4.4 Hz, 1H), 7.38 (s, 1H), 3.85 (s, 3H).	C

310		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.02 (dd, J = 8.5, 2.1 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.49-7.48 (m, 2H), 7.27-7.21 (m, 3H), 6.93 (d, J = 8.4 Hz, 1H), 6.03 (s, 2H), 3.92-3.89 (m, 6H).	C
334		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.70 (d, J = 4.5 Hz, 1H), 8.09 - 7.90 (m, 6H), 7.50 (d, J = 4.5 Hz, 1H), 7.34 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.98 - 3.86 (m, 6H), 1.33 (t, J = 7.1 Hz, 3H).	C

Example 3 – Phosphate-Buffered Saline (PBS) Solubility of Compounds

Materials

[00466] PBS solutions (pH 7.5) were prepared according to the following compositions and stored at 4 ℃.

Reagents	Content
81% 0.0667M Na_2HPO_4	162 mL
19% 0.0667 M NaH_2PO_4	38 mL
NaCl	0.8g

[00467] Test compounds were dissolved in PBS (pH 7.5) at 0.5 mg/mL and vortexed for 90 min. The PBS solution was sequentially filtered through a 0.45, 1.2, 5.0 μM syringe filter.

Analysis

[00468] Concentration of test compounds were determined using LC-MS/MS with appropriate dilution of the samples.

Data

[00469] The solubility of various compounds in PBS are summarized in Table 4 below. Solubility ranges (ng/mL): (A) refers ≥ 10,000 ng/mL; (B) refers to 100 < B < 10,000 ng/mL; and (C) refers to ≤ 100 ng/mL.

Table 4 – PBS Solubility of Compounds					
Cmpd No.	Solubility Range	Cmpd No.	Solubility Range	Cmpd No.	Solubility Range
1	C	2	C	3	C
6	C	7	C	8	C
9	B	10	B	11	C
12	C	14	B	15	C
16	A	17	C	18	C
19	A	21	A	28	C
31	C	32	C	33	C
34	C	36	B	39	C
41	C	42	C	43	C
46	C	47	C	48	C
51	C	55	C	56	C
57	C	58	C	62	B
63	B	65	C	69	A
72	A	73	B	75	A
76	B	85	A	86	A
92	C	96	B	97	B
100	B	105	C	106	C
109	C	114	C	121	C
125	C	126	B	127	C
130	C	131	C	132	C
133	C	135	C	136	C
139	C	140	C	141	C
142	C	144	C	145	B
146	C	147	C	149	A

Table 4 – PBS Solubility of Compounds					
Cmpd No.	Solubility Range	Cmpd No.	Solubility Range	Cmpd No.	Solubility Range
151	A	156	B	157	C
158	C	159	B	160	C
161	B	163	C	164	C
165	C	166	C	167	C
168	C	169	C	170	B
178	A	186	A	204	C
210	B	212	B	256	C
257	C	259	B	271	C
272	C	273	C	274	C
276	C	277	C	280	C
281	C	282	C	283	C
284	B				

Example 4 – Cell-based YFP Assay

Materials and Instrumentations

[00470] Forskolin (Tocris cat. # 1099), Dimethyl sulfoxide (Sigma cat. # D4540), FLUO star Omega microplate reader (BMG Labtech, Ortenberg, Germany), MARS Data Analysis Software (BMG Labtech), GraphPad Prism 5 (GraphPad Software, Inc.)

Cell Culture conditions

[00471] Chinese hamster ovary (CHO-K1) cells expressing human wild type-CFTR and halide sensor YFP-H148Q/I152L were constructed and grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS, 2 mM glutamine, 100 units/ml penicillin and 100 µg/ml streptomycin.

Experimental Procedures

[00472] Chinese hamster ovary (CHO-K1) cells expressing human wild type-CFTR and halide sensor YFP-H148Q/I152L were seeded in 96-well microplate with 2×10^4 cells/well and incubated in 37°C, 48 hours. Then, each well was washed 3 times with PBS and 100 µL PBS was added in each

well. Forskolin, test compounds (100X) were added in each well and incubated in 37°C, 10 minutes. YFP fluorescence signal affected by I^- ion influx through CFTR channel was measured in 37°C, FLUO star Omega microplate reader according to the following steps:

i) basal 2 seconds;

ii) 140 mM I^- solution 100 µL addition to each well;

iii) YFP fluorescence signal measurement start after 6 seconds; and

iv) following 14 seconds signal detection in every 0.4 seconds periods.

[00473] The fluorescent signal of forskolin 20 µM per second was used as 100% activity in data normalization of fluorescent signal in each concentration. Experiments were performed in triplicates and the data was averaged. EC_{50} values were calculated with MARS Data Analysis Software (BMG Labtech) and GraphPad Prism 5.

Data

[00474] The EC_{50} concentration ranges of compounds are summarized in Table 5 below. EC_{50} (nM) concentration ranges: (A) refers to $EC_{50} < 200$ nM; (B) refers to $200 \leq EC_{50} < 2000$ nM; and (C) refers to $EC_{50} \geq 2000$ nM.

Table 5 – Cell-based YFP Assay (EC_{50})

Cmpd No.	Concentration Range	Cmpd No.	Concentration Range	Cmpd No.	Concentration Range
1	A	2	A	3	A
4	B	5	C	6	A
7	B	8	A	9	A
10	A	11	A	12	B
13	B	14	B	15	A
16	C	17	A	18	B
19	C	20	B	21	C
22	C	23	C	24	C
25	C	26	B	27	C
28	A	29	C	30	C
31	A	32	A	33	B
34	A	35	C	36	B
37	C	38	B	39	B

Cmpd No.	Concentration Range	Cmpd No.	Concentration Range	Cmpd No.	Concentration Range
40	C	41	A	42	A
43	A	44	B	45	C
46	A	47	A	48	A
49	B	50	C	51	A
53	B	54	B	55	A
56	A	57	A	58	A
59	A	60	A	61	C
62	B	63	B	64	A
65	A	68	C	69	B
70	C	71	C	72	B
73	B	74	C	75	C
76	B	77	A	78	B
80	C	81	C	82	C
83	C	84	C	85	B
86	B	87	C	88	C
89	C	90	C	91	C
92	A	93	B	94	C
95	C	96	B	97	B
98	C	99	C	100	B
101	C	102	C	103	C
104	C	105	A	106	A
107	C	108	C	109	B
110	B	111	B	112	A
113	A	114	A	115	B
116	B	117	C	118	C
119	B	120	A	121	A

Cmpd No.	Concentration Range	Cmpd No.	Concentration Range	Cmpd No.	Concentration Range
122	A	123	C	124	A
125	A	126	B	127	B
128	A	129	B	130	A
131	A	132	A	133	A
134	A	135	A	136	A
137	B	138	C	139	A
140	A	141	A	142	A
144	A	145	B	146	A
147	A	148	C	149	B
150	C	151	A	152	B
153	B	154	B	155	C
156	A	157	A	158	A
159	B	160	B	161	B
162	C	163	B	164	A
165	B	166	B	167	A
168	B	169	A	170	A
171	A	172	A	173	A
174	A	175	A	176	C
177	C	178	B	179	C
180	C	181	C	182	C
183	B	184	B	185	B
186	A	187	C	188	C
189	A	190	B	191	A
192	A	193	A	194	A
195	B	196	B	197	B
198	A	199	B	200	A

Cmpd No.	Concentration Range	Cmpd No.	Concentration Range	Cmpd No.	Concentration Range
201	C	202	C	203	C
204	A	205	A	206	B
207	B	208	C	209	A
210	A	211	B	212	A
213	C	214	C	215	C
216	C	217	C	218	C
219	C	220	C	221	C
222	C	223	C	224	C
225	C	226	C	227	A
228	A	229	A	230	A
231	C	232	C	233	C
234	C	235	C	236	C
237	C	238	C	239	C
240	C	241	C	242	A
243	B	244	A	245	C
246	B	247	B	248	C
249	C	250	B	251	B
252	C	253	B	254	C
255	A	256	A	257	A
258	A	259	B	260	B
261	B	262	B	263	B
264	C	265	C	266	A
267	A	268	A	269	A
270	A	271	A	272	A
273	A	274	A	275	A
276	A	277	A	278	C

Cmpd No.	Concentration Range	Cmpd No.	Concentration Range	Cmpd No.	Concentration Range
279	C	280	A	281	A
282	A	283	B	284	A
285	A	286	A	287	B
288	C	289	A	290	B
291	C	292	A	293	C
294	C	295	C	296	C
297	C	298	C	299	C
300	C	301	C	302	C
303	C	304	C	305	C
306	C	307	B	308	B
309	A	310	A	311	A
312	A	313	C	314	A
315	C	316	C	317	B
318	B	319	B	320	B
321	B	322	C	323	C
324	C	325	A	326	B
327	A	328	B	329	A
330	B	331	B	332	B
333	C	334	A	335	A
336	B	337	C	338	A
339	C	340	C	341	C
342	B	343	C	344	B
345	C	346	A	347	C
348	B	349	A	350	A
351	A	352	A	353	A
354	A	355	A	356	A

Cmpd No.	Concentration Range	Cmpd No.	Concentration Range	Cmpd No.	Concentration Range
357	B	358	B	359	B
360	B	361	B	362	B
363	A	364	A	365	A
366	A	367	A	368	A
369	A	370	A	371	B
372	B	373	B	374	B
375	A	376	A	377	A
378	A	379	A	380	A
381	A	382	A	383	B
384	A				

Example 5 – Short-circuit current measurement

Materials and Instrumentations

[00475] Forskolin (Tocris cat. # 1099), $CFTR_{inh}$-172 (Tocris cat. # 3430), amphotericin B (Tocris cat. # 6930), dimethyl sulfoxide (Sigma cat. # D4540), EVC4000 Multi-Channel V/I Clamp (World Precision Instruments, Sarasota, FL), PowerLab 4/35 (AD Instruments, Castle Hill, Australia), Labchart Pro 7, GraphPad Prism 5 (GraphPad Software, Inc.).

Cell Culture

[00476] Fisher rat thyroid (FRT) cells expressing human wild type-CFTR were provided by Dr. Alan Verkman (University of California, San Francisco) and grown in DMEM/F12 medium (1:1) supplemented with 10% FBS, 2 mM glutamine, 100 units/ml penicillin and 100 µg/ml streptomycin.

Experimental Procedures

[00477] Snapwell inserts containing CFTR-expressing FRT cells were mounted in Ussing chambers (Physiologic Instruments, San Diego, CA). The apical bath was filled with a half-Cl^- solution and the basolateral bath was filled with HCO_3-buffered solution to generate transepithelial Cl- gradient (apical, 64mM; basolateral, 129mM), and the basolateral membrane was permeabilized with 250 µg/mL amphotericin B. Cells were bathed for a 20 min stabilization period and aerated with 95 % O_2 / 5 % CO_2 at 37 °C. Forskolin, test compounds, and $CFTR_{inh}$-172 were added to the apical and basolateral bath solution. Apical membrane current and short-circuit current were measured with an

EVC4000 Multi-Channel V/I Clamp (World Precision Instruments, Sarasota, FL) and recorded using PowerLab 4/35 (AD Instruments, Castle Hill, Australia). Data were collected and analyzed with ADInstruments acquisition software Labchart Pro 7 software. The sampling rate was 4 Hz. The signal of Forskolin 20 μM was used as 100% activity in data normalization and EC_{50} calculation with GraphPad Prism 5.

Data

[00478] The EC_{50} concentration ranges are summarized in Table 6 below. EC_{50} (nM) concentration ranges: (A) refers to EC_{50} < 200 nM; (B) refers to 200 ≤ EC_{50} <2000 nM; and (C) refers to EC_{50} ≥ 2000 nM.

Table 6 –Short-circuit current measurement (EC_{50})

Cmpd No.	Concentration range	Cmpd No.	Concentration range	Cmpd No.	Concentration range
2	B	3	A	6	A
7	C	8	B	9	C
10	B	11	A	12	C
14	C	15	A	17	A
28	A	31	A	33	C
36	C	41	B	69	C
72	C	78	B	86	C
96	C	97	B	100	B
105	B	106	C	111	C
126	C	127	B	129	C
130	B	131	A	132	B
133	A	135	A	136	A
137	B	140	A	141	A
142	A	144	A	146	A
147	A	149	C	151	B
158	A	159	B	186	B
197	B	198	A	200	A

Table 6 –Short-circuit current measurement (EC_{50})					
Cmpd No.	**Concentration range**	**Cmpd No.**	**Concentration range**	**Cmpd No.**	**Concentration range**
205	A	210	B	212	C
256	A	257	B	259	B
271	A	274	A	277	A
280	A	285	A	289	A

Example 6 – CFTR Modulators in Scopolamine induced Tear Volume Reduction Model

[00479] This example demonstrates the change in tear volume in mice that were dosed with CFTR modulator compounds in the tear volume reduction model as induced by Scopolamine.

Materials

[00480] Seven-week old C57BL/6 female mice were used.

[00481] Scopolamine hydrobromide was purchased from Sigma Aldrich (Cat No. S0929), dissolved in saline, and sterilized prior to use.

[00482] Zone-Quick phenol red thread was obtained from Menicon.

[00483] Phosphate buffered saline (PBS, pH 7.5, 17% 0.0667 M NaH_2PO_4/83% 0.066 M Na_2HPO_4) was prepared.

[00484] The test compounds used in this experiment were dissolved in PBS containing 1% of surfactant.

[00485] Scopolamine (0.2 ml of 2.5 mg/mL solution) was injected subcutaneously 3 times a day to induce a decrease in the tear volume in the mouse. At the same time, the ophthalmic solution of test compounds or vehicle were topically administered onto both eyes 3 times a day. Tear volume was measured by phenol red thread before dosing (basal level) and 1 hour after the last administration of scopolamine and ophthalmic solution. The results were obtained by measuring the length of the phenol red thread turning red by tears. The schedule of study is expressed as FIG. 1.

Results

[00486] On day 2, the amount of tear in mice injected with scopolamine decreased to about 50% of the basal level. This tear reduction showed a tendency to alleviate in mice administered with some test compounds compared to that of vehicle-treated mice.

[00487] The results are summarized in Table 7 as the ratio of tear volume of test compound treatment group to that of vehicle treatment group. If the test compound was evaluated twice, the average value was used.

Table 7 – Tear Volume Reduction Model Results

Cmpd No.	**Ratio of tear volume (test compound to vehicle)**	**Cmpd No.**	**Ratio of tear volume (test compound to vehicle)**	**Cmpd No.**	**Ratio of tear volume (test compound to vehicle)**
2	1.40	3	1.20	6	1.58
9	1.16	10	1.89	15	1.29
36	1.23	69	0.76	72	1.06
96	1.35	97	0.95	126	0.97
140	1.48	141	1.34	144	1.18
147	1.03	149	1.26	151	1.40
158	1.40	159	2.11	186	1.05
197	1.18	205	1.12	210	1.43
212	1.43	257	1.16	259	0.94
271	1.17	272	1.14	273	0.80
274	1.07	276	1.21	280	1.32

Example 7 – Human Phosphodiesterase 4 (PDE4) Inhibition

Experimental Procedures

[00488] Chinese Human recombinant PDE4A1A, PDE4B1, PDE4C1 and PDE4D2 are respectively expressed in each host cell (insect Sf9 cells, BPS Bioscience). Preincubation of 10 μM test compounds or vehicle was proceeded with 20 ng/ml PDE4A1A or 4 ng/ml PDE4B1 or 8 ng/ml PDE4C1 or 5 ng/ml PDE4D2 enzyme in Tris-HCl buffer pH 7.2 for 15 minutes at 25°C. 100 nM fluorescein (FAM) labeled cAMP for another 30 minutes incubation period was added in order to initiate the enzymatic reaction and addition of IMAP binding solution was followed for its termination. Specifically, IMAP complexes with phosphate groups on nucleotide monophosphate generated from cyclic nucleotides through PDE activity. The amount of complex formed is determined by reading spectrofluorimetrical signal at 470 nm/525 nm.

Data

[00489] The PDE4 inhibitory effects are summarized in Table 8 below. PDE4 inhibition (% at 10 uM) ranges: (A) refers to ≥ 80% inhibition; (B) refers to 50% ≤ inhibition <80%; and (C) refers to <50% inhibition.

Table 8 – Human Phosphodiesterase 4 (hPDE4) inhibition

Cmpd No.	% inhibition range at 10 uM			
	PDE4A1A	PDE4B1	PDE4C1	PDE4D2
7	C	C	C	C
10	A	A	A	A
11	A	A	A	A
12	A	B	B	B
15	A	A	A	A
33	B	B	C	B
41	A	A	A	A
96	A	A	B	A
97	A	A	A	A
105	A	A	A	A
129	A	A	A	A
135	A	A	A	A
136	A	A	A	A
144	A	A	A	A
147	A	A	A	A
151	A	A	A	A
192	A	A	A	A
194	A	A	A	A
198	A	A	A	A
205	A	A	A	A
210	A	A	A	A
239	C	C	C	C
257	A	A	A	A
287	B	B	C	B
323	C	B	C	C
352	A	A	A	A
355	A	A	A	A
380	A	A	B	A
384	A	A	B	A

Example 8 – Human peripheral blood mononuclear cell (PBMC) cytokine release study

Materials and Instrumentations

[00490] Human peripheral blood mononuclear cells (PBMCs) (ATCC, Cat #PCS-800-011, Lot#81201311, USA), Lipopolysaccharides (LPS) from Escherichia coli (Sigma Aldrich, Cat #L2654, Batch #0000089955, USA), Apremilast (Selleckchem, Cat #S8034, Lot #S803401, USA), Xiidra (Shire, Cat #NDC-54092-606-01, USA), Human Magplex Luminex – 8 plex (R&D systems, Cat #LXSAHM-08, Lot #L142868, USA), Cell counting kit-8 (Sigma Aldrich, Cat #96992, Lot #BCCF5335, USA).

Compounds

[00491] The compounds evaluated in this study were compound Nos. 41, 105, 135, 144, 147, 151, 194, 198, 205 and 210.

Experimental Procedures

1. Cell Culture

[00492] Human PBMCs frozen in a cryopreserved states were thawed, washed with Dulbecco's PBS solution containing 5% human serum, and seeded onto a 96 well plate at a density of 2×10^5 cells/well with culture RPMI1640 media containing 5% human serum. They were incubated at 37°C in a CO_2 incubator for 1 hr.

2. Compound Treatment

[00493] After 1 hr, PBMCs were treated with Cmpd. 41, Cmpd. 105, Cmpd. 135, Cmpd. 144, Cmpd. 147, Cmpd. 151, Cmpd. 194, Cmpd. 198, Cmpd. 205, and Cmpd. 210 (1 and 10 µM), positive compound Apremilast (10 µM), and Xiidra (100 µM). Then, these were incubated at 37°C in a CO_2 incubator for 1hr. After compound treatment, PBMCs were treated with stimulants (LPS 5 µg/ml) and then incubated at 37°C in a CO_2 incubator for 18 hr.

3. CCK-8 Assay

[00494] After collecting the cell supernatant, 100 µl of media and 10 µl of CCK-8 were added to the cells in a 96 well plate and incubated in a CO_2 incubator at 37°C for 24 hr. After 24 hr, the absorbance at 450 nm was measured using a microplate reader.

4. Luminex Assay

[00495] Luminex assay was used to measure 8 cytokines and chemokines. The 1:2, 1:100 diluted cell supernatant and serial dilution of the standard were dispensed into a 96 well plate at 50 µl/well. Then, the microparticle cocktail of antibody-coated magnetic beads (Human Magplex Luminex – 8 plex) was dispensed at 50 µl/well and incubated at room temperature for 2 hr using a horizontal orbital shaker at 800 rpm. The beads were washed using a magnetic device to prevent loss. The biotin-antibody was dispensed in 50 µl of each well and incubated at room temperature for 1 hr using the shaker at 800 rpm. After washing, streptavidin-PE was added at 50 µl/well and incubated at room temperature for 30 min using the shaker under the same conditions. Finally, after washing, wash

buffer (100 µl/well) was added to the 96 well plate and the 96 well plate was incubated using the shaker for 2 min. The LuminexTM 200 was set according to the manufacturer's protocol. The data was calculated with a standard five-parameter logistic nonlinear regression analysis (xPonent software 4.2, USA).

5. Statistical Analysis

[00496] All values are presented as ± standard error of the mean (SEM) and difference at the $p<0.05$ level was considered statistically significant. Statistical analyses were performed using the IBM SPSS™ Statistics 26 software. The statistical significance of the results was analyzed using one-way ANOVA followed by LSD post-hoc analysis.

Data

[00497] TNF-alpha level increased significantly in the LPS-treated group compared to the control group. Xiidra, 1 µM Cmpd. 105, 1 µM Cmpd. 144, or 1 µM Cmpd. 151 treatment led to moderate reduction of TNF-alpha levels. Apremilast, Cmpd. 41, 10 µM Cmpd. 105, Cmpd. 135, 10 µM Cmpd. 144, Cmpd. 147, 10 µM Cmpd. 151, Cmpd. 194, Cmpd. 198, Cmpd. 205, or Cmpd. 210 treatment led to very low TNF-alpha levels compared to the LPS-treated group (FIG. 2).

[00498] IFN-gamma level increased significantly in the LPS-treated group compared to the control group. Xiidra, 1 µM Cmpd. 105, or 1 µM Cmpd. 144 treatment led to moderate reduction in IFN gamma levels compared to the LPS-treated group. Other treatment groups showed relatively lower IFN gamma levels. IFN-gamma level of groups treated with 10 µM Cmpd. 105, 10 µM Cmpd. 147, 10 µM Cmpd. 151, 10 µM Cmpd. 198, 10 µM Cmpd. 205, and Cmpd. 210 was significantly lower compared to the Apremilast-treated group (FIG. 3).

[00499] CCL3/MIP-1 alpha level increased significantly in the LPS-treated group compared to the control group. Xiidra, 1 µM Cmpd. 105, or 1 µM Cmpd. 144 treatment led to mild reduction in CCL3/MIP-1 alpha levels compared to the LPS-treated group. Other treatment groups showed relatively lower IFN gamma levels. CCL3/MIP-1 alpha level of groups treated with 10 µM Cmpd. 105, 10 µM Cmpd. 135, 10 µM Cmpd. 144, 10 µM Cmpd. 147, 10 µM Cmpd. 151, 10 µM, Cmpd. 194, 10 µM Cmpd. 198, 1 µM Cmpd. 205, and 10 µM Cmpd. 210 was significantly lower compared to the Apremilast-treated group (FIG. 4).

[00500] The PBMC data was normalized to cell viability. Cell viability of the LPS-treated group was significantly higher compared to the control group. Cell viability of the group treated with 10 µM Cmpd. 194 showed the lowest cell viability among all tested groups (FIG. 5).

[00501] In summary, the subject compounds reduced the LPS-stimulated increase in TNF-alpha, IFN-gamma, and CCL3/MIP-1 release, and this effect was stronger at high concentration. These results indicate that the subject compounds have anti-inflammatory properties by downregulation of TNF-alpha, IFN-gamma, and CCL3/MIP-1 release, which may have potential therapeutic effects in the treatment of inflammatory diseases.

Example 9 – Liposaccharide-induced cytokine release mouse model

Materials and Instrumentation

[00502] Lipopolysaccharide (LPS) (L4391, Sigma), Mouse IL-10 Immuno-PCR-IQELISA (LSBio, LS-F253-1), Mouse TNF-alpha ELISA kit (raybiotech, ELM-TNFa), Microplate Reader (TECAN)

Animals

[00503] Seven-week-old BALB/c female mice were used for this study.

Compounds

[00504] The compounds evaluated in this study were compound Nos. 198, 205 and 210.

Experimental Procedures

1. Animal experiments and cytokine analysis

[00505] Each of the test compounds (Cmpd. 198, Cmpd. 205, and Cmpd. 210) and vehicle were administrated to mice by intraperitoneal injection at a volume of 5 mL/kg body weight (n=5). Test compounds were dissolved in a formulation composed of 2% Tween 80 (v/v), 10% PEG 400 (v/v) with saline. One hour after administration of test compounds or vehicle, LPS (1 mg/kg) in saline were injected intravenously. After 1.5 hr, mice were anesthetized by isoflurane and blood was collected via heart puncture. Serum samples were obtained by centrifugation and stored at -80°C. TNF-alpha in serum of each mouse was detected using ELISA kits (raybiotech; ELM-TNFa) according to the manufacture's protocol.

2. Statistical analysis

[00506] All values were presented as ± standard error of the mean (SEM). Statistical analyses were performed using Prism (Graphpad, version 5). The statistical significance of the results was analyzed using T-test. P value<0.05 was considered statistically significant.

Data

[00507] The level of TNF-alpha in the serum from LPS only treated mice were elevated compared to that of control mice. Pretreatments of Cmpd. 210 at 1 and 10 mg/kg, Cmpd. 205 at 10 mg/kg, and Cmpd. 198 at 10 mg/kg tended to inhibit LPS-induced increase in serum TNF-alpha (Table 9).

[00508] These results suggest that compounds of this disclosure have potential anti-inflammatory effect through inhibition of LPS-induced TNF-alpha release.

Table 9. TNF-alpha level in the serum

Group			Mean value of TNF-α	Standard deviation
LPS treated	Pre-treatment	Dose		
Not treated	Vehicle	0	Not detected	0
LPS	Vehicle	0	546.7	602
	Cmpd. 198	1 mg/kg	552.1	673.8
		10 mg/kg	16.2	25.6
	Cmpd. 205	1 mg/kg	Not detected	0
		10 mg/kg	Not detected	0
	Cmpd. 210	1 mg/kg	392.4	406.7
		10 mg/kg	65.4	146.2

Example 10 – Imiquimod-induced psoriasis mouse model

Materials and Instrumentations

[00509] 5% IMQ (imiquimod) cream (Aldara), Vaseline (Unilever), hair removal cream (Beauty Formulas), Isoflurane (Hana Pharm Co., Ltd.)

Animals

[00510] Eight-week-old BALB/c female mice were used for this study.

Compounds

[00511] The compounds evaluated in this study were compound Nos. 41, 205, 144, 3, 257, 15, and 352.

Experimental Procedures

1. Animal experiment

[00512] In order to induce the psoriasis-like inflammation in the mice, 62.5 mg of 5% IMQ cream were applied onto the pre-shaved back skin once daily for 9 days. 62.5 mg of the ointments including each test compound or placebo ointment were treated 4 h prior to each IMQ application. The severity of psoriasis-like inflammation was scored using the following scoring system: The scores of skin plaque (0-3), erythema (0-3), thickness (0-3), and total psoriasis area and severity index (PASI) score (0-9) of each mouse were recorded daily. On day 9, mice were sacrificed after final scoring. Further, skin tissues were collected and fixed with 10% formalin solution for further histological analysis.

2. Histological analysis

[00513] The skin tissue fixed with 10% formalin solution is processed through the general tissue treatment process, then paraffin-embedded, and then stained with Hematoxylin & Eosin (H&E)

using a paraffin block and tissue section. The stained tissues were observed under an optical microscope (BX61, Olympus, Japan) and were photographed (DP80, Olympus, Japan). For histopathological quantitative analysis, epidermal thickness and dermal thickness were measured, and the degree of inflammatory cell infiltration was quantitatively analyzed by counting inflammatory cells in a randomly selected 1 mm^2 area. As the quantitative analysis tool, Image-Pro software (Media cybernetics, USA) was used.

3. Statistical analysis

[00514] All values of PASI scoring were presented as ± standard deviation (SD). Statistical analyses were performed using Prism (Graphpad, version 5). The statistical significance of the results was analyzed using T-test. P value<0.05 was considered statistically significant. ***P<0.001 compared with Normal control. ##P<0.01, ###P<0.001 compared with Vehicle-treated group. Quantitative data of histological analysis were expressed as mean ± SD, and statistical significance between groups was analyzed using statistical program GraphPad prism (Ver. 9.0). After analysis was performed by one-way ANOVA test, a post-hoc test was performed with fisher's multiple comparison test. P value<0.05 was considered statistically significant. *p<0.05 vs. IMQ only group; **p<0.01 vs. IMQ only group; #p<0.05 vs. Vehicle-treated group; ##p<0.01 vs. Vehicle-treated group.

Data

[00515] The scores for total PASI, erythema, thickness, and skin plaque (scales) are depicted in FIGs 6A-6D. Total PASI score was significantly improved in groups treated with ointment containing compound Nos. 41, 205, 144, 3, 257, 15, or 352 at day 9 (FIG. 6A). The scores for total PASI, erythema, thickness, and skin plaque (scales) of each compound during the whole experiment period are shown in FIGs7A-13D. In particular, all PASI scores of compound 352 from day 2 to day 9 showed significant improvement compared to the vehicle-treated group (FIGs 13A-13D). Other compounds, such as compound 15 and compound 144, also significantly improved the total PASI score compared to the vehicle-treated group on most days of the study period (FIGs 12A-12D for compound 15, and FIGs 9A-9D for compound 144). In the histological analysis, characteristic lesions of psoriasis characterized by hyperkeratosis and inflammatory cell infiltration were identified in the disease groups IMQ-only and vehicle-treated groups (FIGs. 14-16). In addition, FIGs. 17-26 illustrate that histopathological changes due to IMQ-induced psoriasis were significantly improved in the several of the compound treated groups. For example, the number of infiltrated inflammatory cells was significantly reduced in the compound 41, compound 205, and compound 3-treated groups compared to the vehicle-treated group (FIG. 26), indicating that the subject compounds have the potential to inhibit the infiltration of inflammatory cells. These results suggest that the subject compounds have potential therapeutic effect as a topical ointment for the inflammatory skin disease such as psoriasis.

7. EQUIVALENTS AND INCORPORATION BY REFERENCE

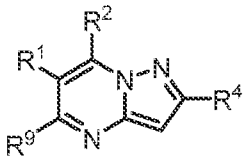
[00516] While the invention has been particularly shown and described with reference to a preferred embodiment and various alternate embodiments, it will be understood by persons skilled in the relevant art that various changes in form and details can be made therein without departing from the spirit and scope of the invention.

[00517] All references, issued patents and patent applications cited within the body of the instant specification are herein incorporated by reference in their entirety, for all purposes.

CLAIMS

What is claimed is:

1. A method of treating an inflammatory disease, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (Ia):

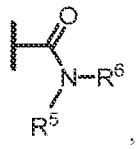
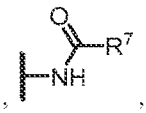
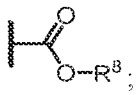


(Ia)

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

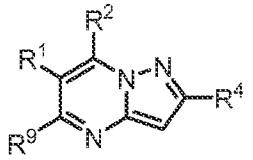
R^9 is selected from H and halogen.

2. The method of claim 1, wherein the inflammatory disease is selected from chronic obstructive pulmonary disease (COPD), asthma, inflammatory airway disease, psoriasis, psoriatic disorder, atopic

dermatitis, inflammatory bowel disease (IBD), rheumatoid arthritis, ankylosing spondylitis, neuroinflammation, and conjunctivitis.

3. The method of claim 1 or 2, wherein the inflammatory disease is an inflammatory skin disease.

4. A method of inhibiting activity of PDE4 in a biological system or sample by contacting with a compound of formula (Ia):

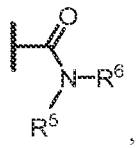
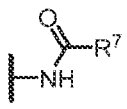
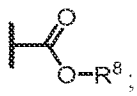


(Ia)

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

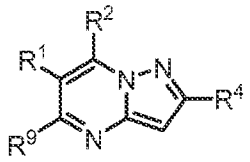
R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

R^9 is selected from H and halogen.

5. A pharmaceutical composition for treating an inflammatory disease, comprising a therapeutically

effective amount of a compound of formula (Ia):

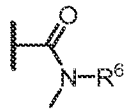
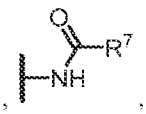
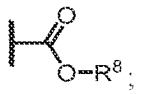


(Ia)

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

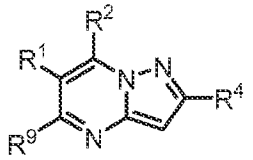
R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

R^9 is selected from H and halogen.

6. The composition of claim 5, wherein the inflammatory disease is selected from chronic obstructive pulmonary disease (COPD), asthma, inflammatory airway disease, psoriasis, psoriatic disorder, atopic dermatitis, inflammatory bowel disease (IBD), rheumatoid arthritis, ankylosing spondylitis, neuroinflammation, and conjunctivitis.

7. The composition of claim 5 or 6, wherein the inflammatory disease is an inflammatory skin disease.

8. A pharmaceutical composition for inhibiting activity of PDE4, comprising a therapeutically effective amount of a compound of of formula (Ia):

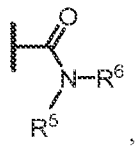
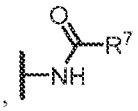
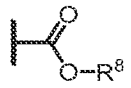


(Ia)

or a pharmaceutically acceptable salt, a solvate, a hydrate, a prodrug, or a stereoisomer thereof, wherein:

R^1 is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^2 is selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^4 is selected from  ,  , and  ;

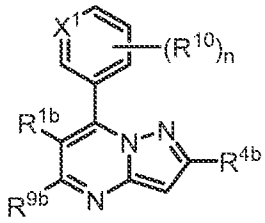
R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl; and

R^9 is selected from H and halogen.

9. The method according to any one of claims 1-4 or the composition of any one of claims 5-8, wherein the compound is of formula (Ib):

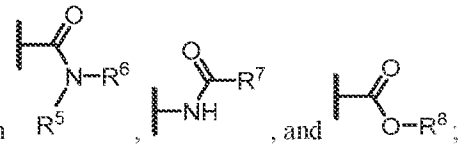


(Ib)

wherein:

X^1 is $CR^{10'}$ or N;

R^{1b} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4b} is selected from  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

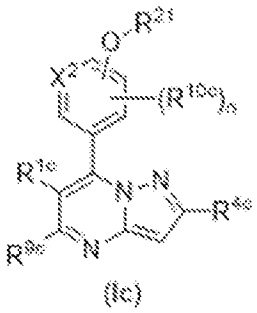
R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

R^{9b} is selected from H and halogen;

each R^{10} and $R^{10'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 4.

10. The method or composition of claim 9, wherein the compound is of formula (Ic):



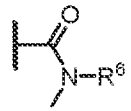
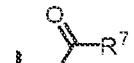
(Ic)

wherein:

X^2 is $CR^{10c'}$ or N;

R^{21} is selected from H, and optionally substituted (C_1-C_{10})alkyl; optionally substituted acyl; optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{1c} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4c} is selected from  ,  , and  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle; or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

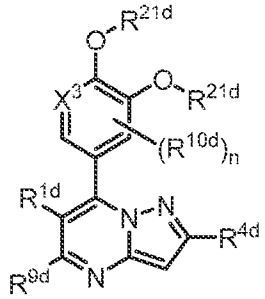
R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

R^{9c} is selected from H and halogen;

each R^{10c} and $R^{10c'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 3.

11. The method or composition of claim 10, wherein the compound is of formula (Id):



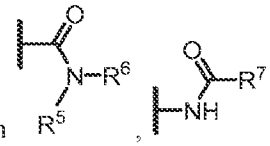
(Id)

wherein:

X^3 is $CR^{10d'}$ or N;

each R^{21d} is independently selected from H, and optionally substituted (C_1-C_{10})alkyl; optionally substituted acyl; optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{1d} is selected from H, halogen, optionally substituted aryl, optionally substituted (C_1-C_{10})alkyl, and optionally substituted (C_1-C_{10})alkoxy;

R^{4d} is selected from  ;

R^5 and R^6 are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^5 and R^6 together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle;

R^7 is selected from NR^5R^6, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;

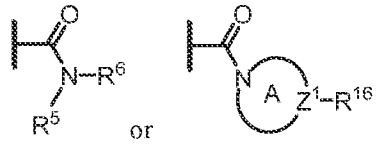
R^8 is selected from H and optionally substituted (C_1-C_{10})alkyl;

R^{9d} is selected from H and halogen;

each R^{10d} and $R^{10d'}$ is independently selected from H, OH, NH_2, NO_2, halogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and substituted amino; and

n is 0 to 2.

12. The method or composition of any one of claims 9 to 11, wherein any of R^4-R^{4d} is



wherein:

ring A is an optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle;

Z^1 is CR^{14} or N, where R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle; and

R^{16} is selected from H, halogen, $-OR^{22a}$, $-C(O)R^{22b}$, $-CO_2R^{22c}$, and $-C(O)NR^{50}R^{60}$, $-NR^{50}R^{60}$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy;

R^{22a}, R^{22b}, and R^{22c} are independently selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle; and

R^{50} and R^{60} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

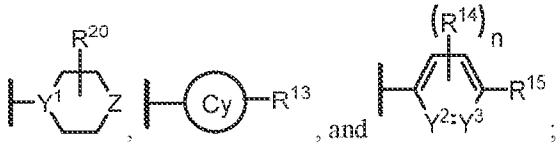
or R^{50} and R^{60} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted heterocycle, or an optionally substituted heteroaryl.

13. The method or composition of claim 12, wherein:

the A ring is an optionally substituted piperazine, pyrrolidine, or azetidine; or

the A ring is an optionally substituted piperidine, wherein when the A ring is piperidine R^{16} comprises at least one cyclic group selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocycle, optionally substituted heterocycle.

14. The method or composition of claim 12, wherein R^5 is H or Me, and R^6 is selected from:



wherein:

Y^1, Y^2, and Y^3 are independently selected from CR^{14} and N;

Z is selected from O, S, CHR^{11}, and NR^{12};

n is 0 to 4;

R^{11} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2a}, $C(O)R^{2b}$, CO_2R^{2c}, $C(O)NR^5R^6$, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, and optionally substituted heterocycle;

R^{12} is selected from H, NH_2, halogen, $C(O)R^{2d}$, CO_2R^{2e}, $C(O)NR^5R^6$, and optionally substituted (C_1-C_5)alkyl;

is selected from optionally substituted (C_1-C_6)alkyl-cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic (C_4-C_{10})carbocycle, and optionally substituted monocyclic or bicyclic (C_4-C_{10})heterocycle;

R^{13} is selected from H, NH_2, CN, CH_2NH_2, NO_2, halogen, OR^{2f}, $C(O)R^{2g}$, CO_2R^{2h}, $C(O)NR^5R^6$, NR^5R^6, $NHC(O)R^2$, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy, and optionally substituted heterocycle;

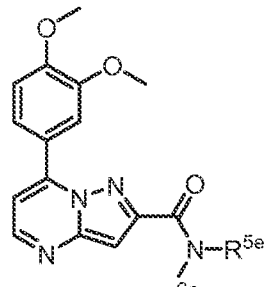
R^{14} is selected from H, OH, NH_2, CN, CF_3, OCF_3, CH_2NH_2, halogen, CO_2R^2, $C(O)NR^5R^6$, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted carbocycle, and optionally substituted heterocycle;

R^{15} is selected from H, halogen, $NHC(O)R^{2i}$, OR^{2j}, $C(O)R^{2k}$, $OC(O)R^{2l}$ CO_2R^{2m}, $C(O)NR^5R^6$, NR^5R^6 optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted cycloalkyl, and optionally substituted heterocycle;

R^{20} is selected from H, halogen, optionally substituted (C_1-C_5)alkyl, optionally substituted (C_1-C_5)alkoxy, optionally substituted carbocycle, and optionally substituted heterocycle; and

R^{2a}-R^{2m} are independently selected from H, optionally substituted (C_1-C_{10}) alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycle, and the optional substituents on alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle are independently selected from: H, OH, NH_2, NO_2, OCF_3, CF_3, halogen, heterocycle, heteroaryl, optionally substituted amino, optionally substituted (C_1-C_5)alkyl, and optionally substituted (C_1-C_5)alkoxy.

15. The method or composition of any one of claims 11-14, wherein the compound is of formula (Ie):

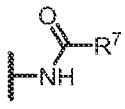


(Ie)

wherein:

R^{5e} and R^{6e} are independently selected from H, optionally substituted (C_1-C_{10})alkyl, optionally substituted (C_1-C_{10})alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

or R^{5e} and R^{6e} together with the nitrogen atom to which they are attached are cyclically linked to form an optionally substituted monocyclic or bicyclic heterocycle.

16. The method or composition of any one of claims 9 to 11, wherein any of R^4-R^{4d} is 
.

17. The method or composition of any one of claims 9 to 16, wherein the compound is of Table 1.

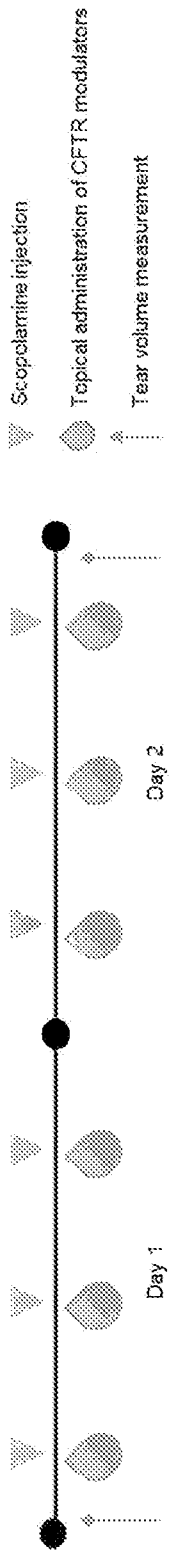

Scopolamine injection
Topical administration of CFTR modulators
Tear volume measurement
Day 2
Day 1

FIG. 1

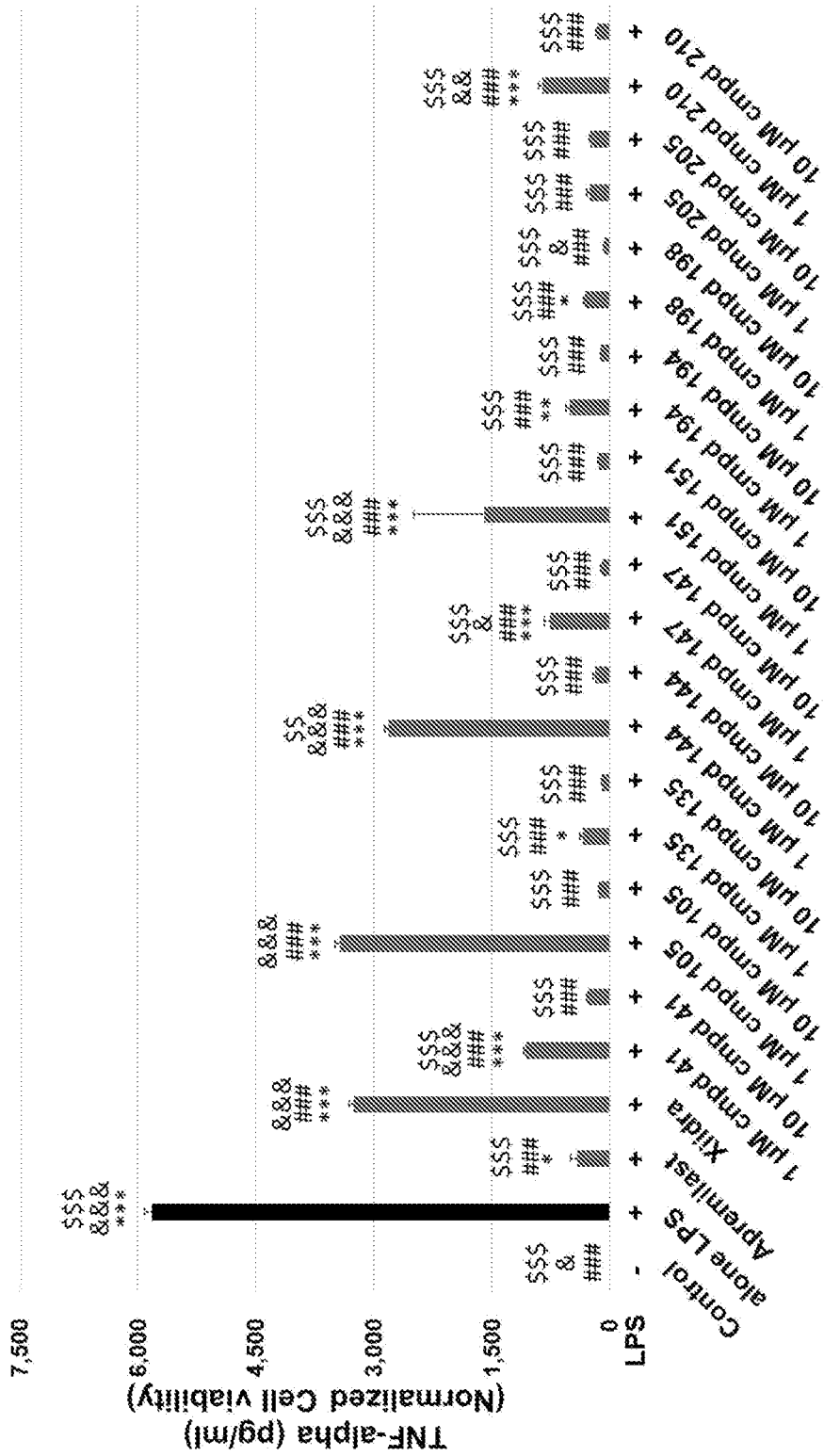

TNF-alpha (pg/ml)
(Normalized Cell viability)
7,500
6,000
4,500
3,000
1,500
0
LPS
Control
alone LPS
Apremilast
Xilidra
1 µM cmpd 41
10 µM cmpd 41
1 µM cmpd 105
10 µM cmpd 105
1 µM cmpd 135
10 µM cmpd 135
1 µM cmpd 144
10 µM cmpd 144
1 µM cmpd 147
10 µM cmpd 147
1 µM cmpd 151
10 µM cmpd 151
1 µM cmpd 194
10 µM cmpd 194
1 µM cmpd 198
10 µM cmpd 198
1 µM cmpd 205
10 µM cmpd 205
1 µM cmpd 210
10 µM cmpd 210

FIG. 2

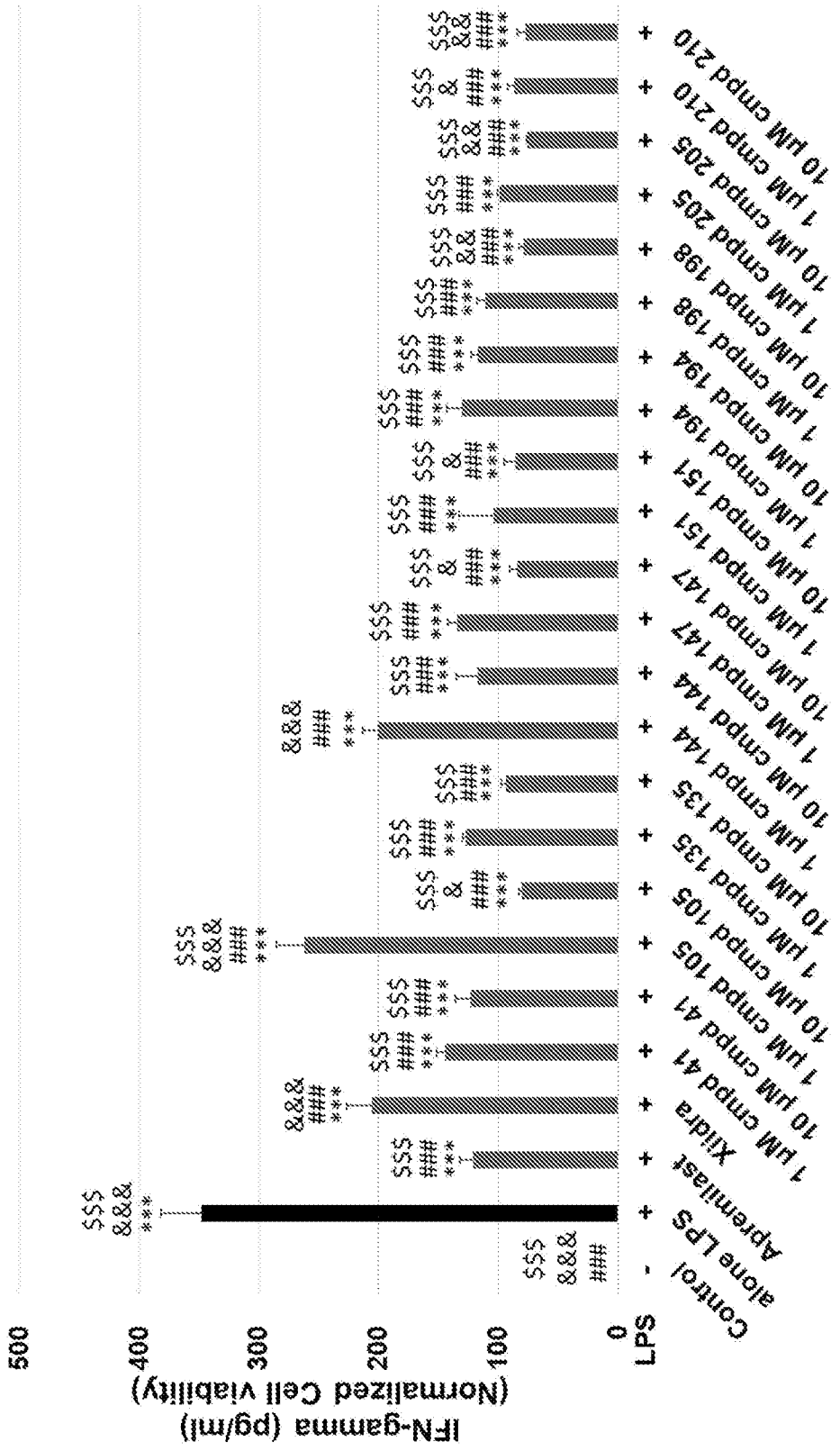

IFN-gamma (pg/ml)
(Normalized Cell viability)
500
400
300
200
100
0
LPS
Control
alone LPS
Apremilast
Xilidra
1 uM cmpd 41
10 uM cmpd 41
1 uM cmpd 105
10 uM cmpd 105
1 uM cmpd 135
10 uM cmpd 135
1 uM cmpd 144
10 uM cmpd 144
1 uM cmpd 147
10 uM cmpd 147
1 uM cmpd 151
10 uM cmpd 151
1 uM cmpd 194
10 uM cmpd 194
1 uM cmpd 198
10 uM cmpd 198
1 uM cmpd 205
10 uM cmpd 205
1 uM cmpd 210
10 uM cmpd 210

FIG. 3

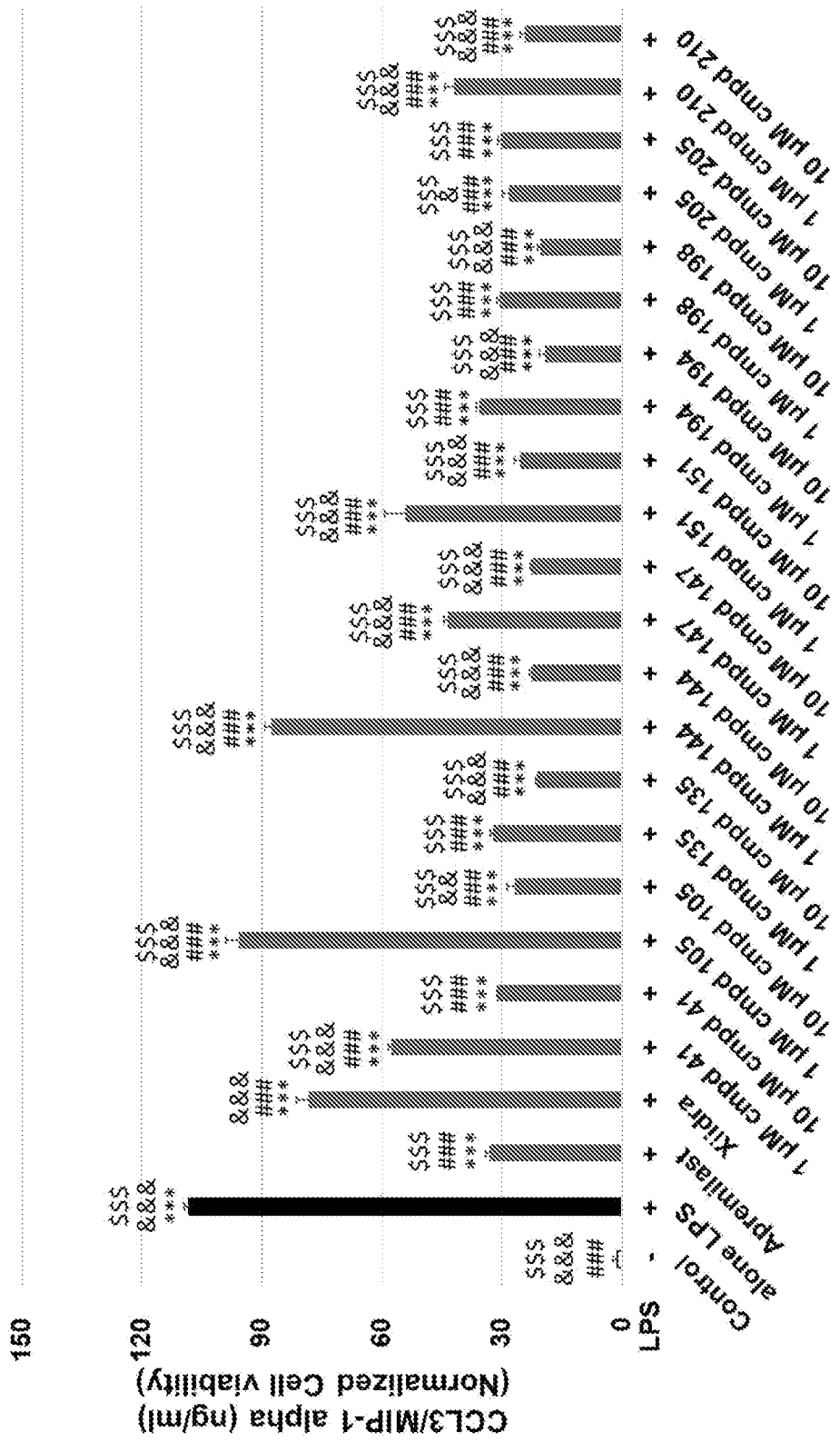

CCL3/MIP-1 alpha (ng/ml)
(Normalized Cell viability)
150
120
90
60
30
0
LPS
Control
alone LPS
Apremilast
Xilidra
1 uM cmpd 41
10 uM cmpd 41
1 uM cmpd 105
10 uM cmpd 105
1 uM cmpd 135
10 uM cmpd 135
1 uM cmpd 144
10 uM cmpd 144
1 uM cmpd 147
10 uM cmpd 147
1 uM cmpd 151
10 uM cmpd 151
1 uM cmpd 194
10 uM cmpd 194
1 uM cmpd 198
10 uM cmpd 198
1 uM cmpd 205
10 uM cmpd 205
1 uM cmpd 210
10 uM cmpd 210

FIG. 4

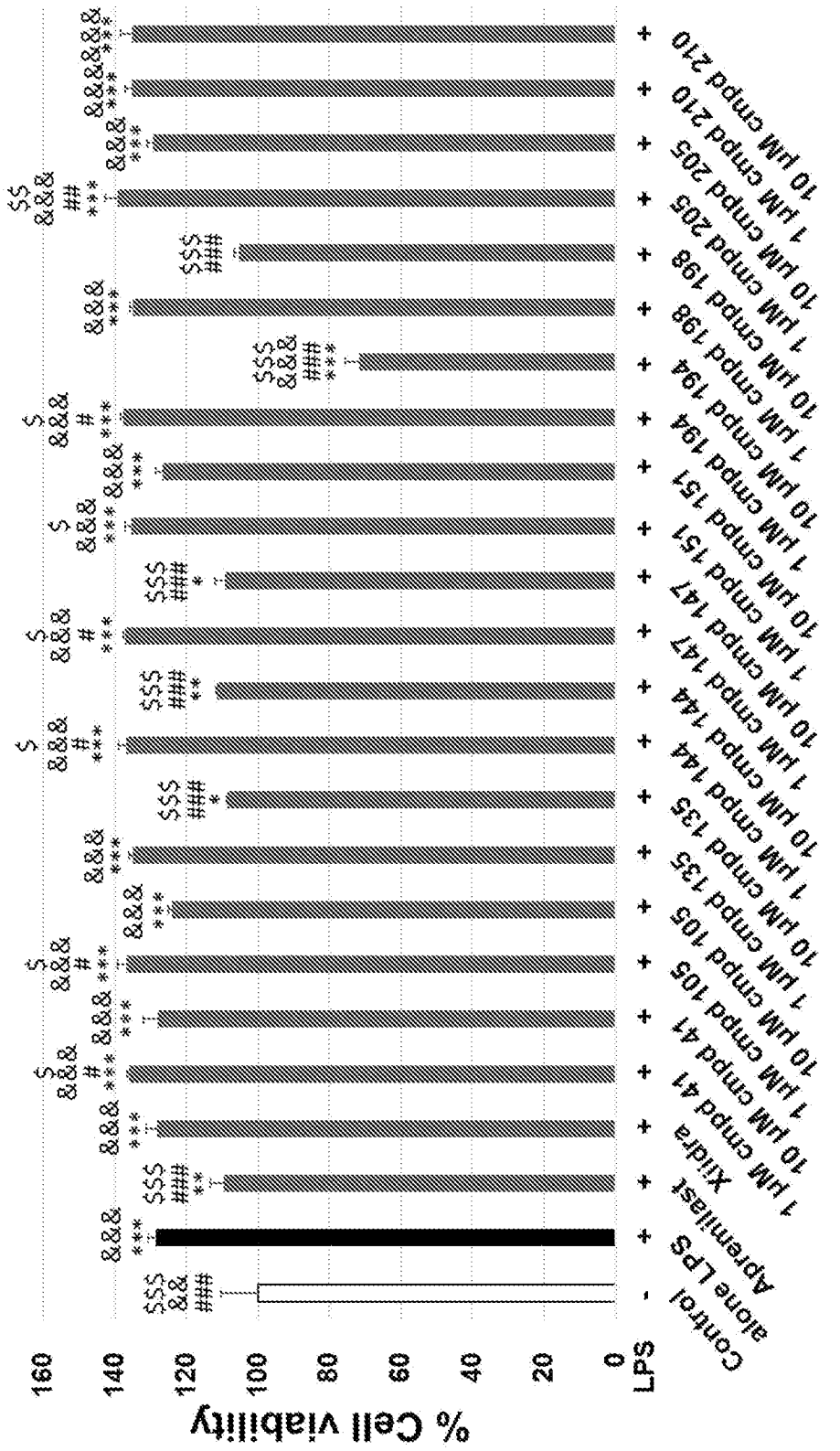

% Cell viability
160
140
120
100
80
60
40
20
0
LPS
Control
alone LPS
Apremilast
Xildra
1 µM cmpd 41
10 µM cmpd 41
1 µM cmpd 105
10 µM cmpd 105
1 µM cmpd 135
10 µM cmpd 135
1 µM cmpd 144
10 µM cmpd 144
1 µM cmpd 147
10 µM cmpd 147
1 µM cmpd 151
10 µM cmpd 151
1 µM cmpd 194
10 µM cmpd 194
1 µM cmpd 198
10 µM cmpd 198
1 µM cmpd 205
10 µM cmpd 205
1 µM cmpd 210
10 µM cmpd 210

FIG. 5

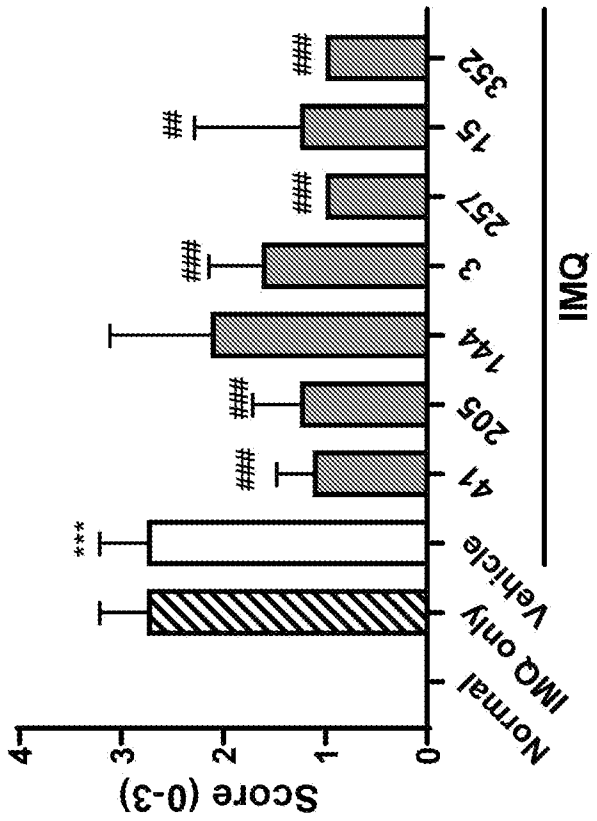

Score (0-3)
0
1
2
3
4
Normal
IMQ only
Vehicle
4
7
20
5
14
4
3
25
7
15
35
2
IMQ
***
#
#
#
#
#
#
#
#

FIG. 6B

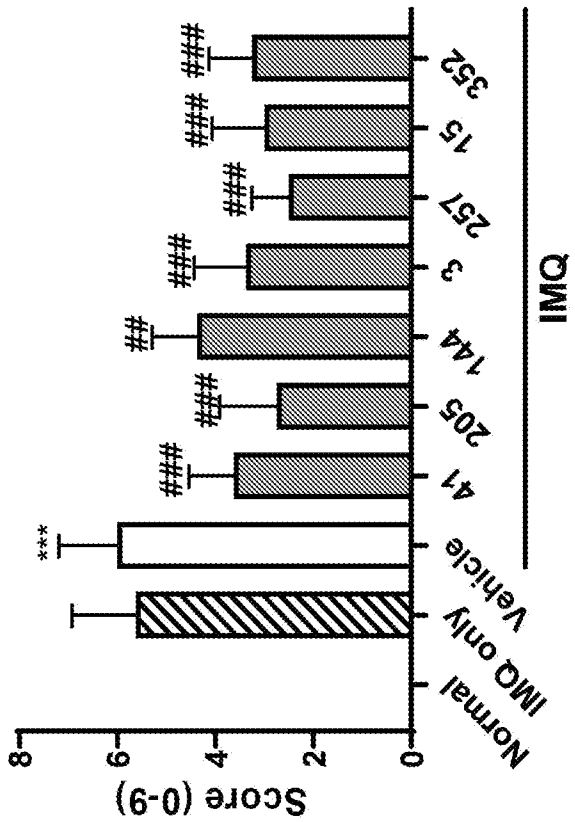

Score (0-9)
0
2
4
6
8
Normal
IMQ only
Vehicle
4
7
20
5
14
4
3
25
7
15
35
2
IMQ
***
#
#
#
#
#
#
#
#

FIG. 6A

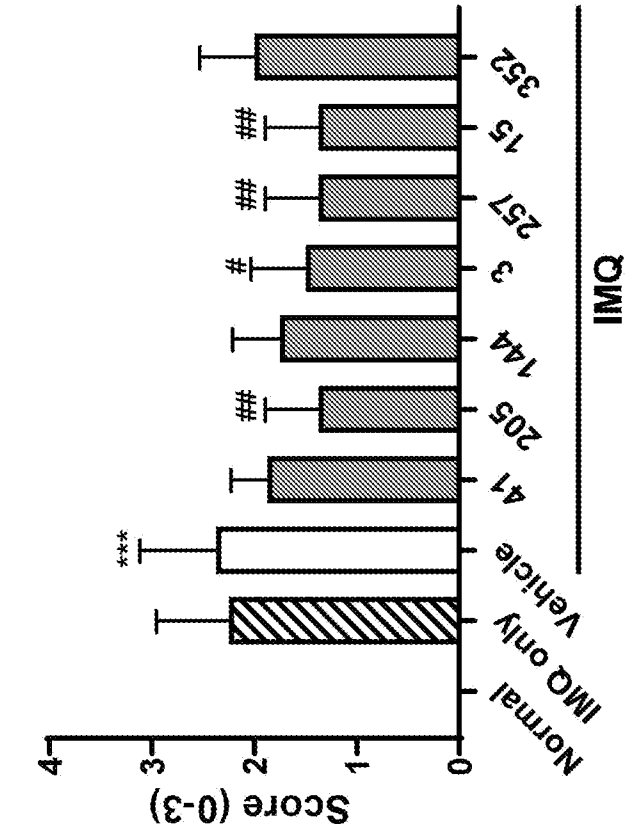

Score (0-3)
0
1
2
3
4
Normal
IMQ only
Vehicle
41
205
144
3
257
15
352
IMQ
***
##
##
#
##
##

FIG. 6D

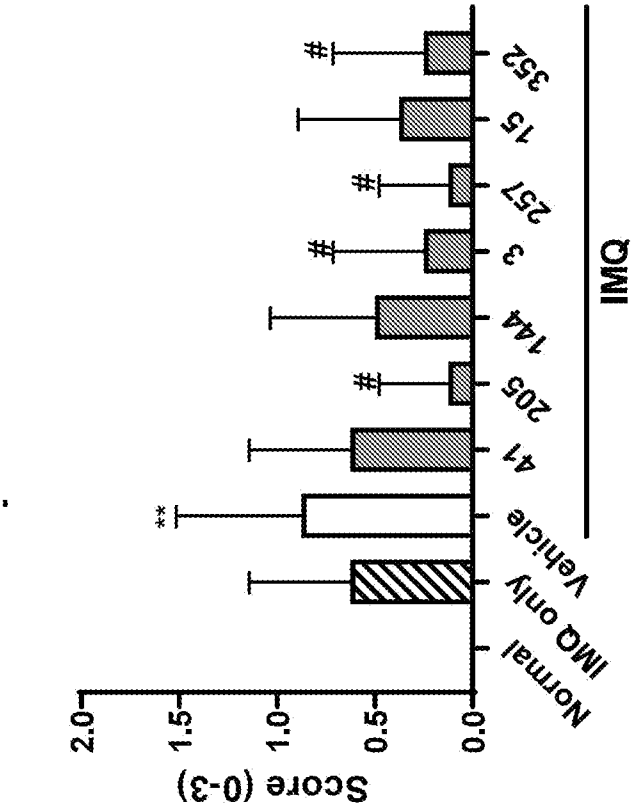

Score (0-3)
0.0
0.5
1.0
1.5
2.0
Normal
IMQ only
Vehicle
41
205
144
3
257
15
352
IMQ
**
#
#
#
#
#

FIG. 6C

FIG. 7A

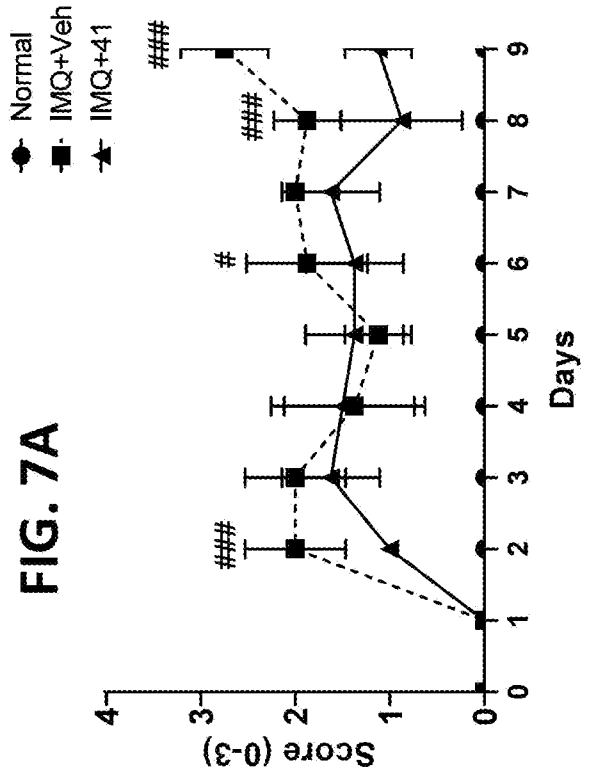


FIG. 7B

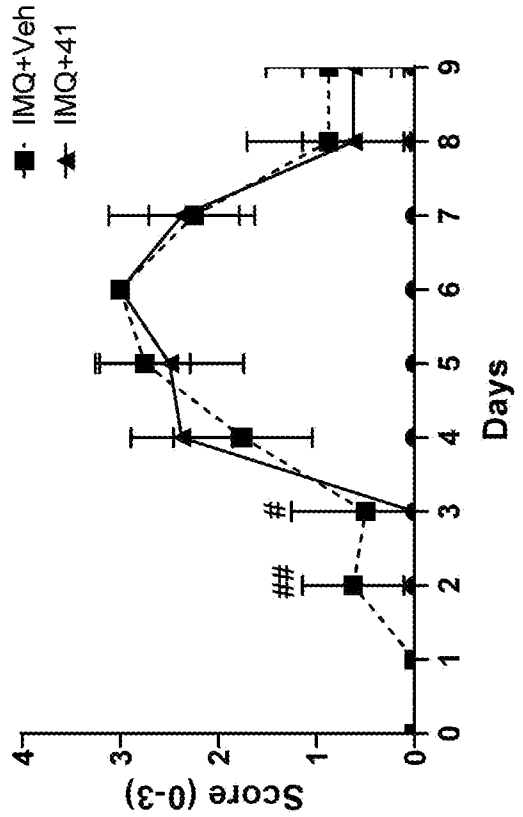


FIG. 7C

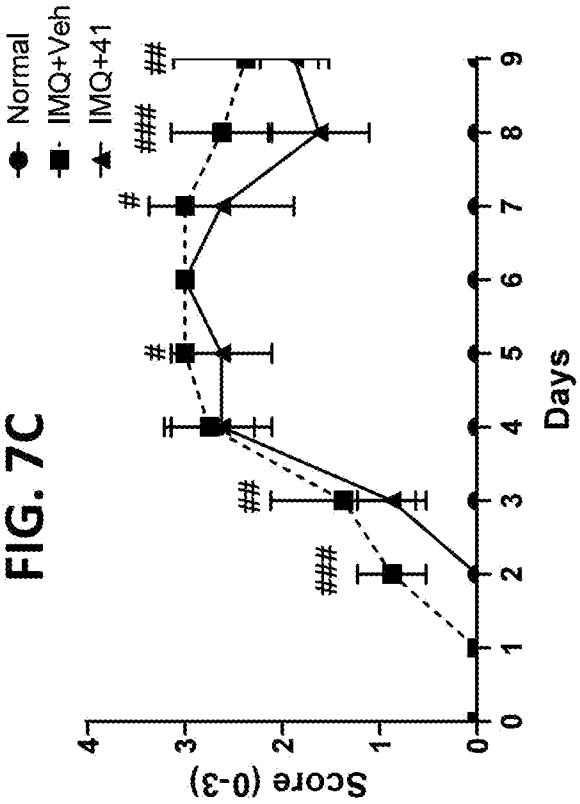


FIG. 7D

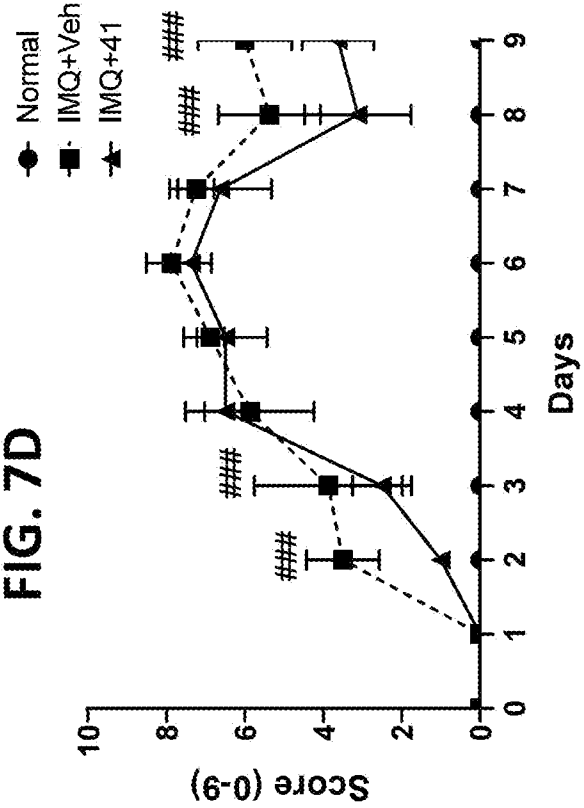


FIG. 8A

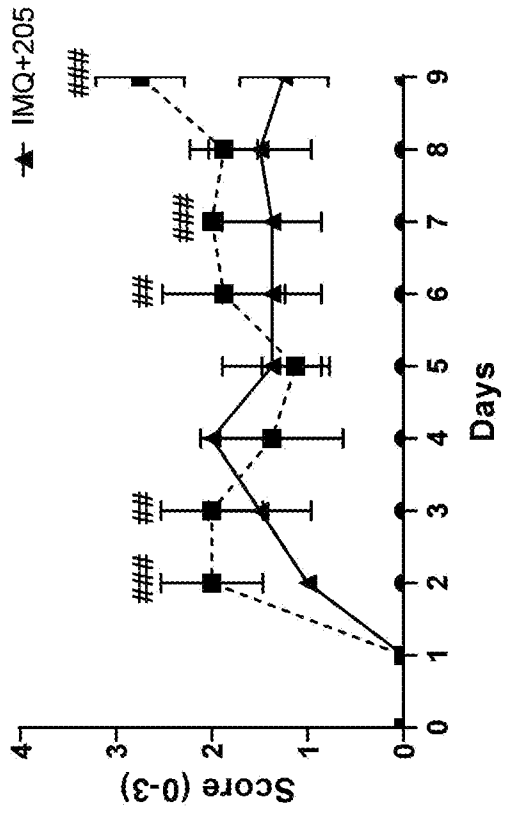


FIG. 8B

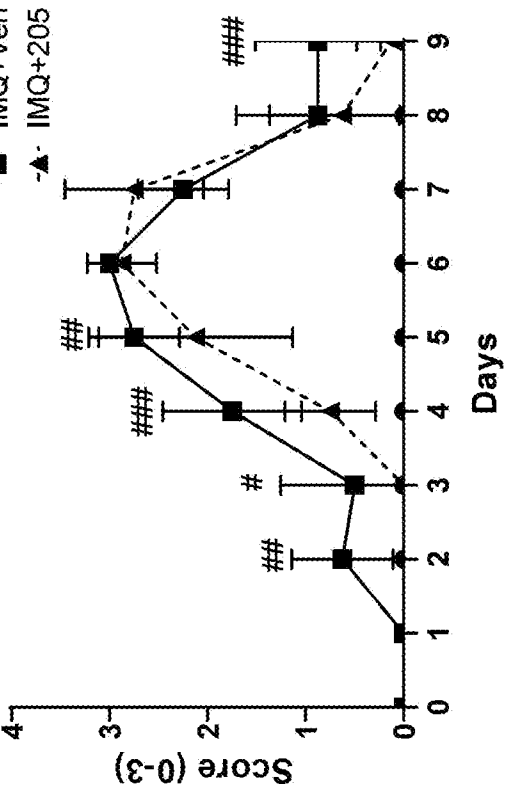


FIG. 8C

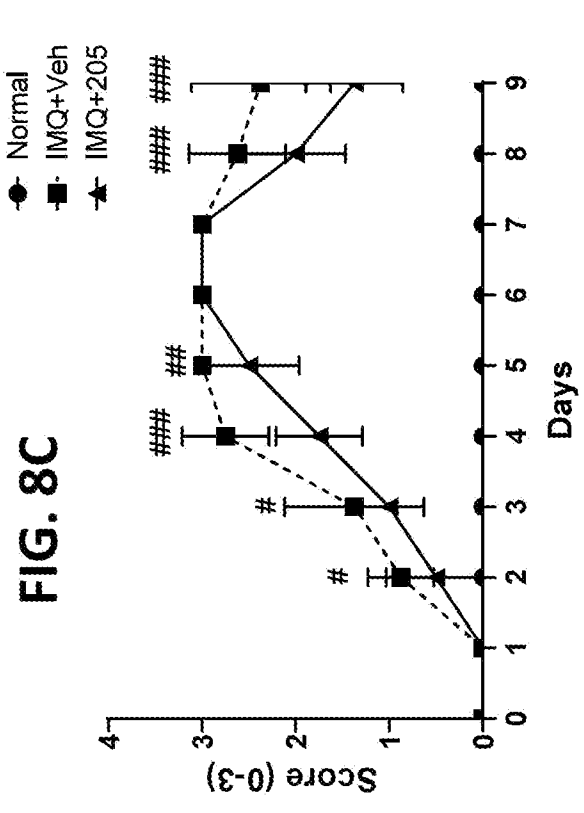
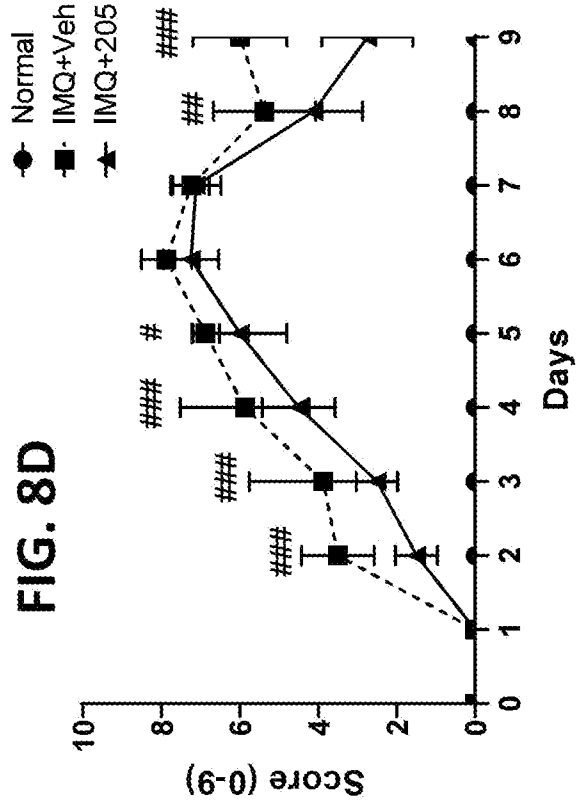


FIG. 8D



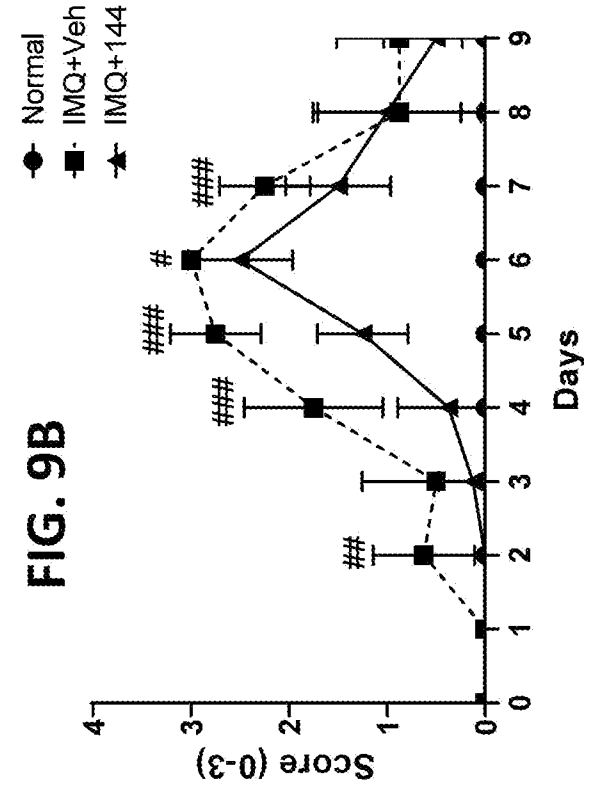


FIG. 9B

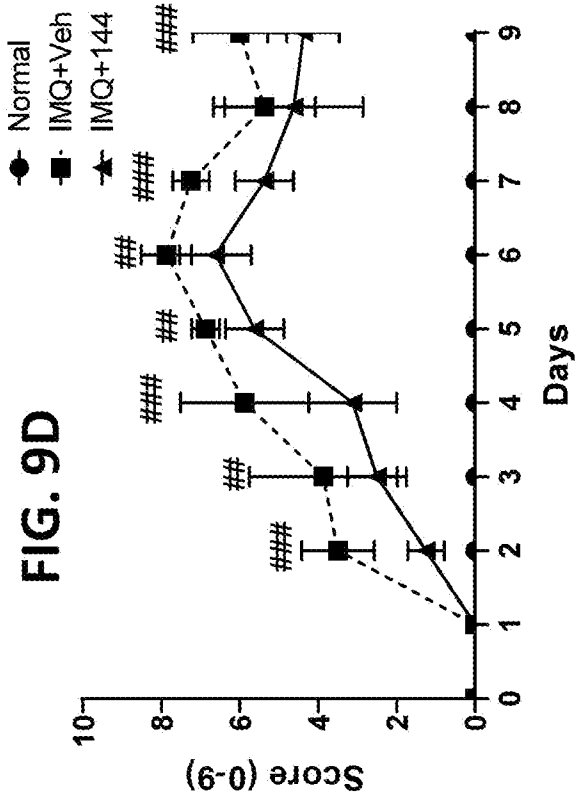


FIG. 9D

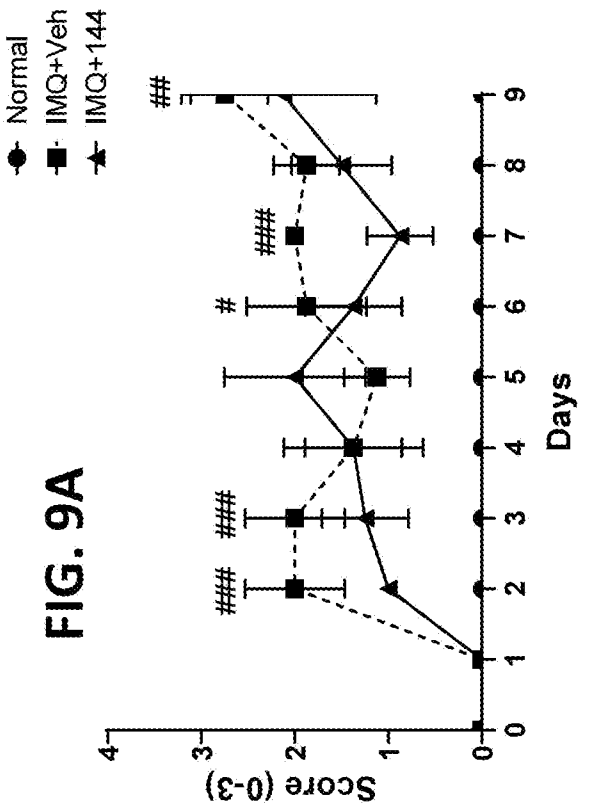


FIG. 9A

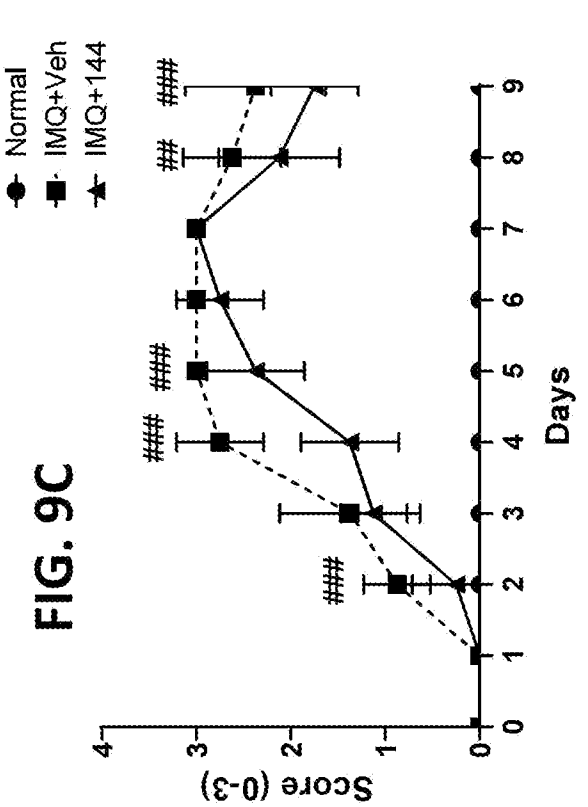


FIG. 9C

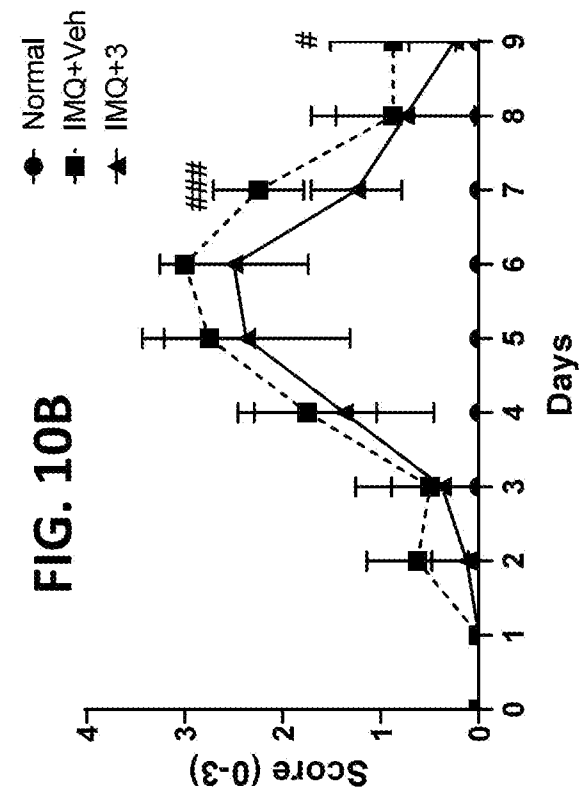


FIG. 10B

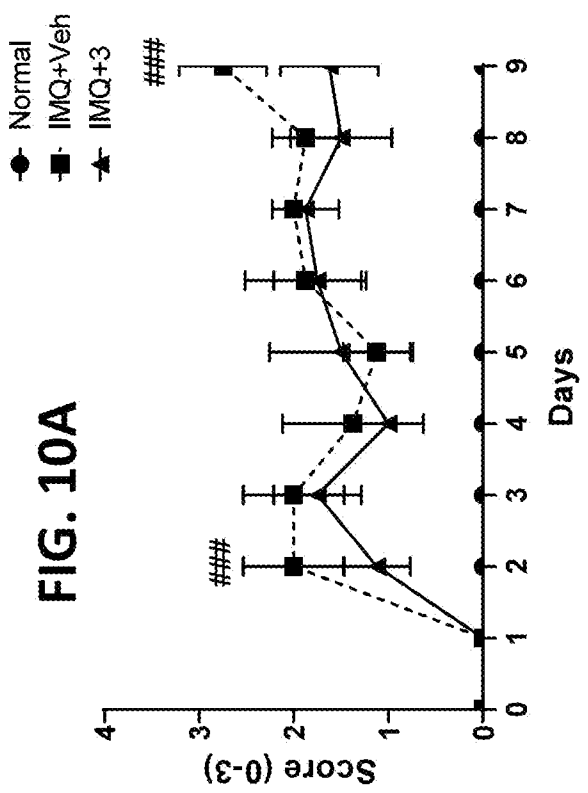


FIG. 10A

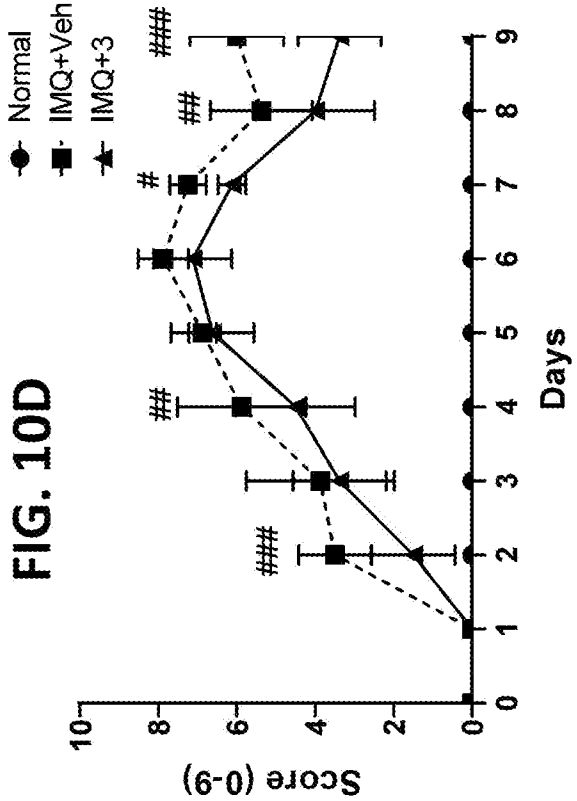


FIG. 10D

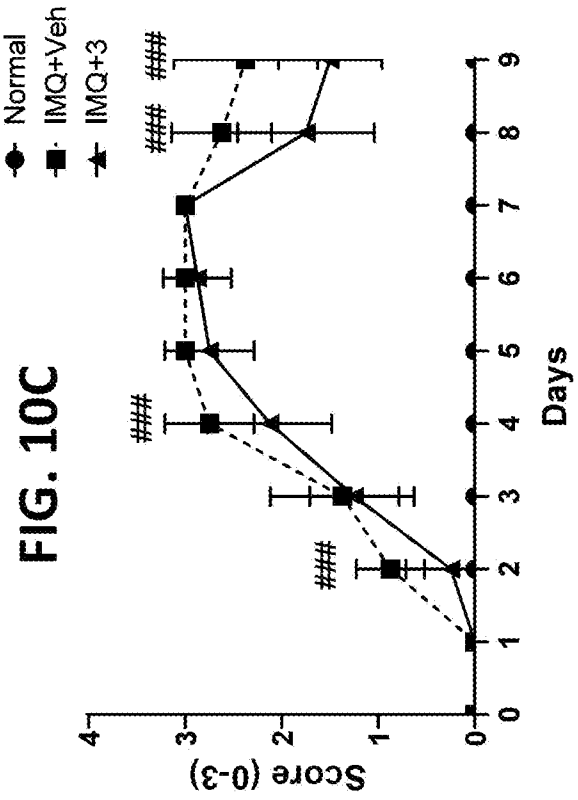


FIG. 10C

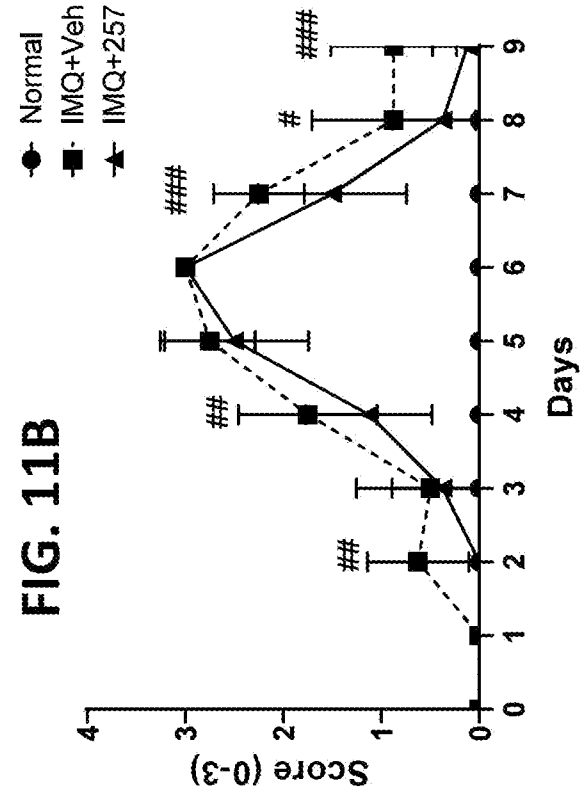


FIG. 11A

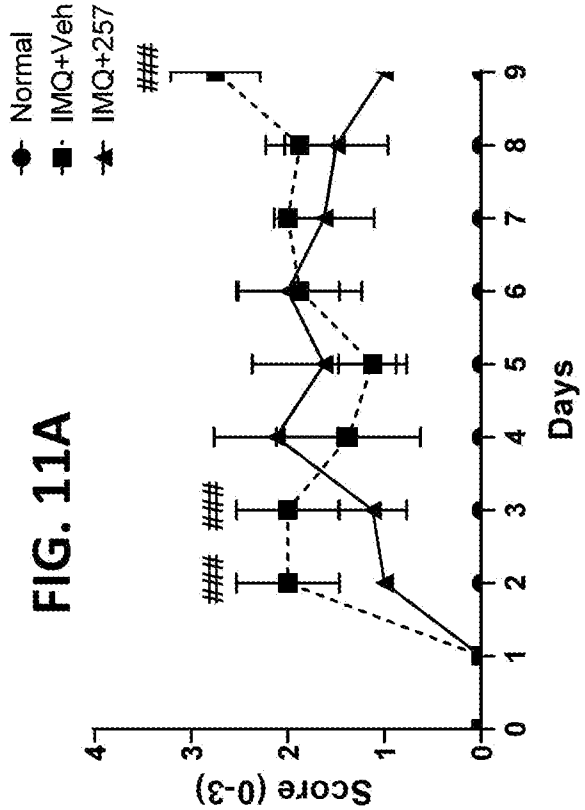


FIG. 11B

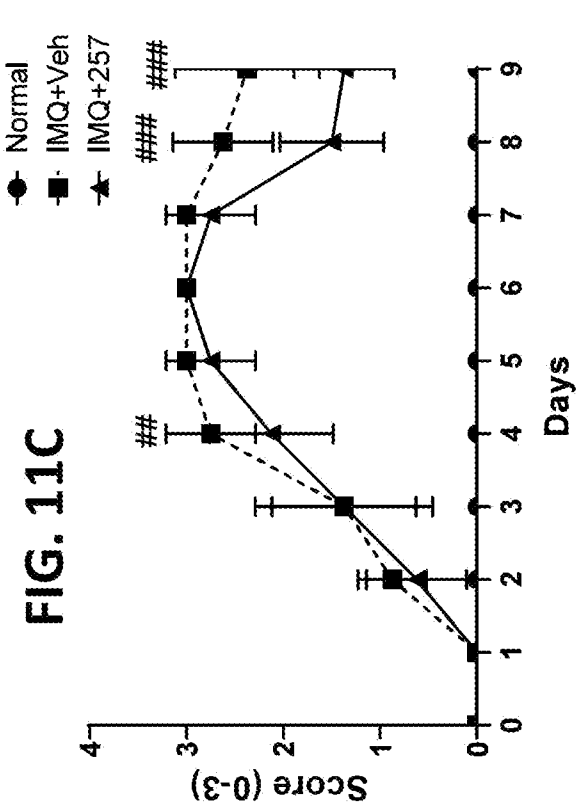


FIG. 11C

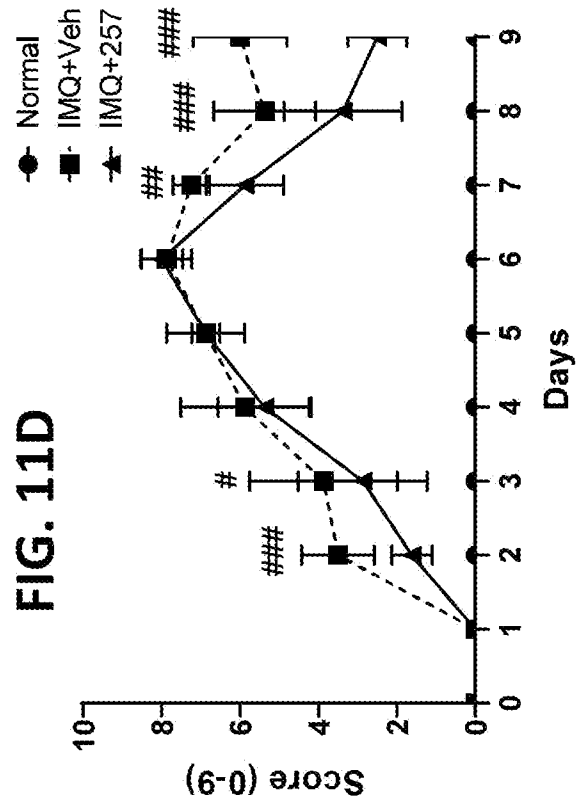


FIG. 11D

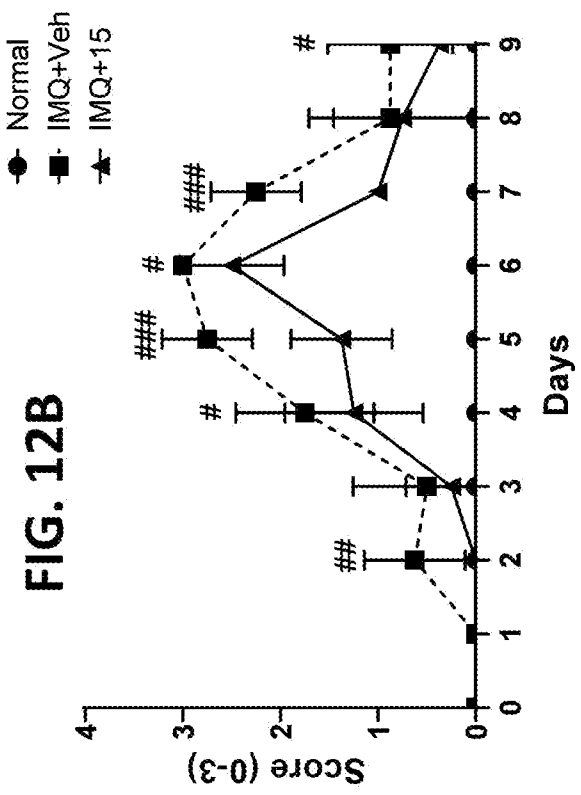


FIG. 12B

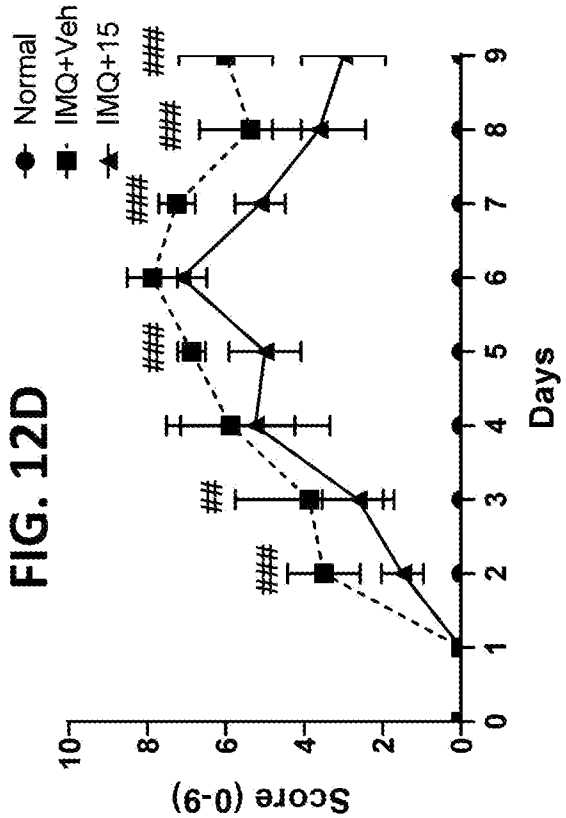


FIG. 12D

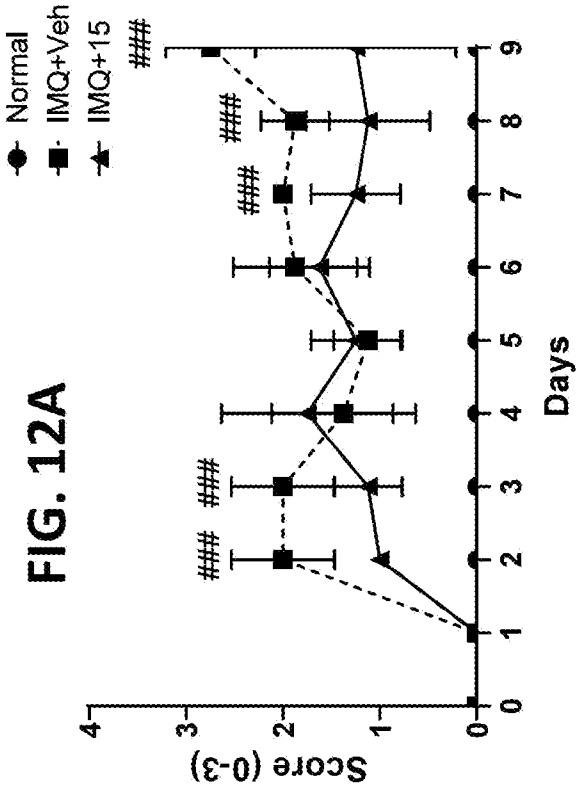


FIG. 12A

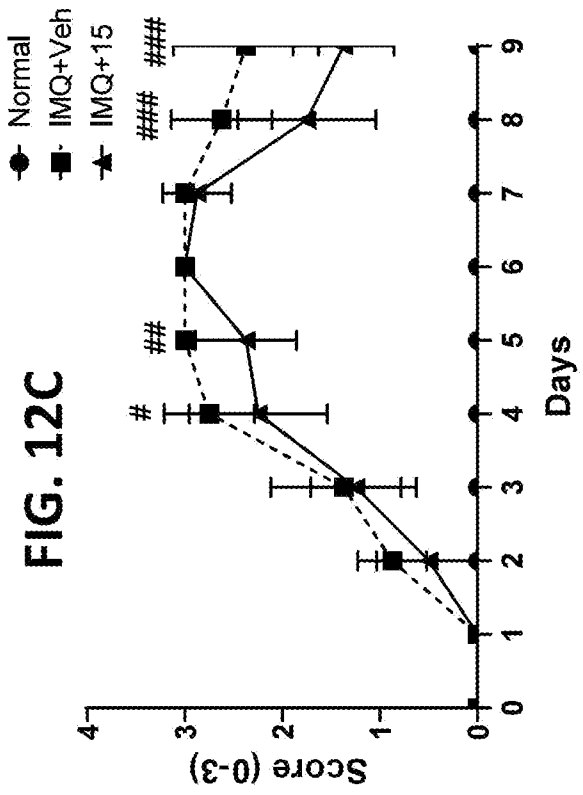


FIG. 12C

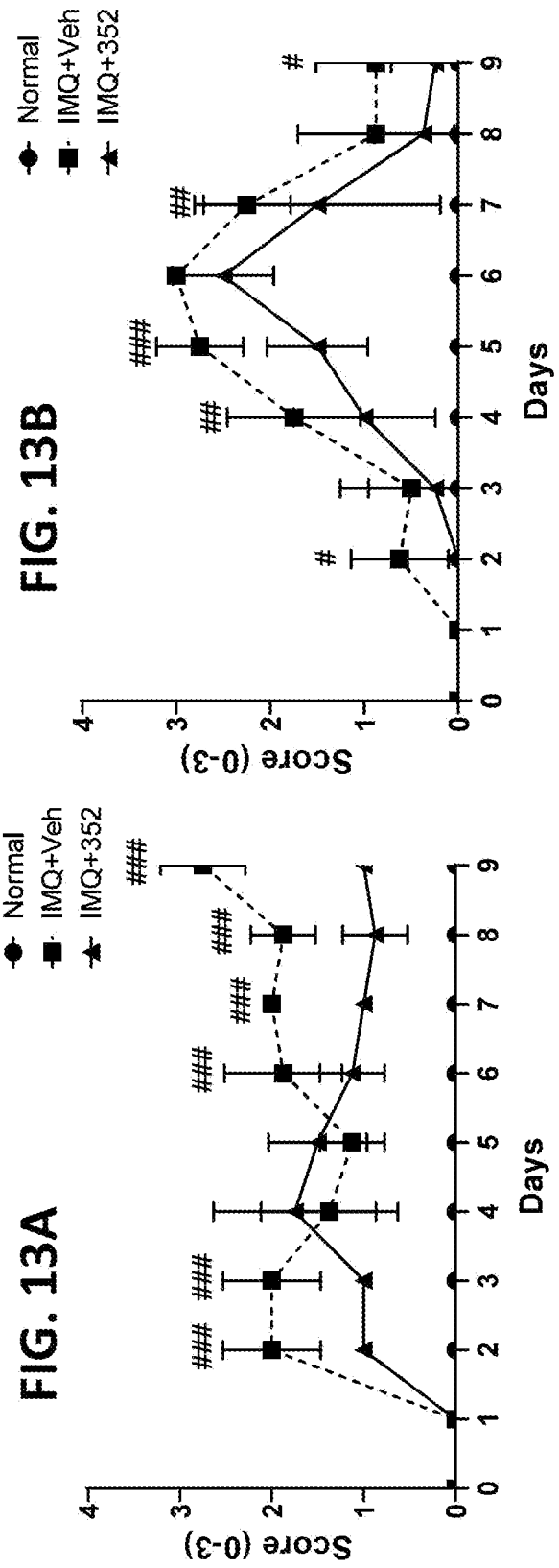


FIG. 13A

FIG. 13B

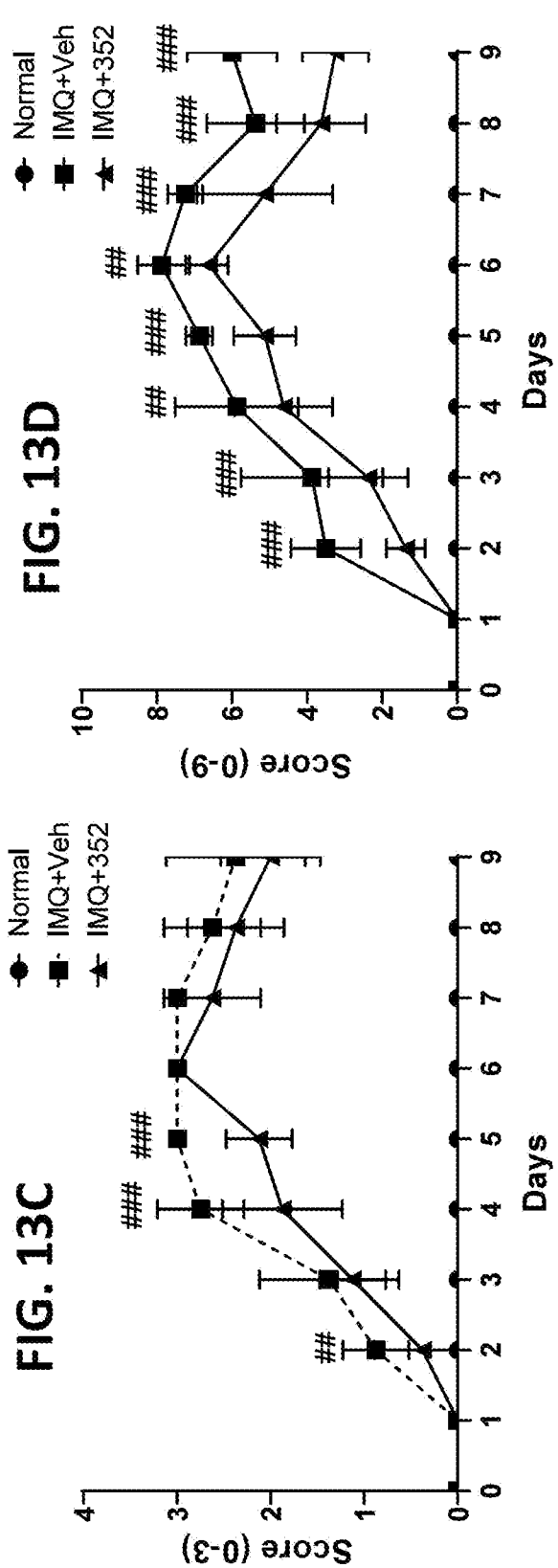


FIG. 13C

FIG. 13D

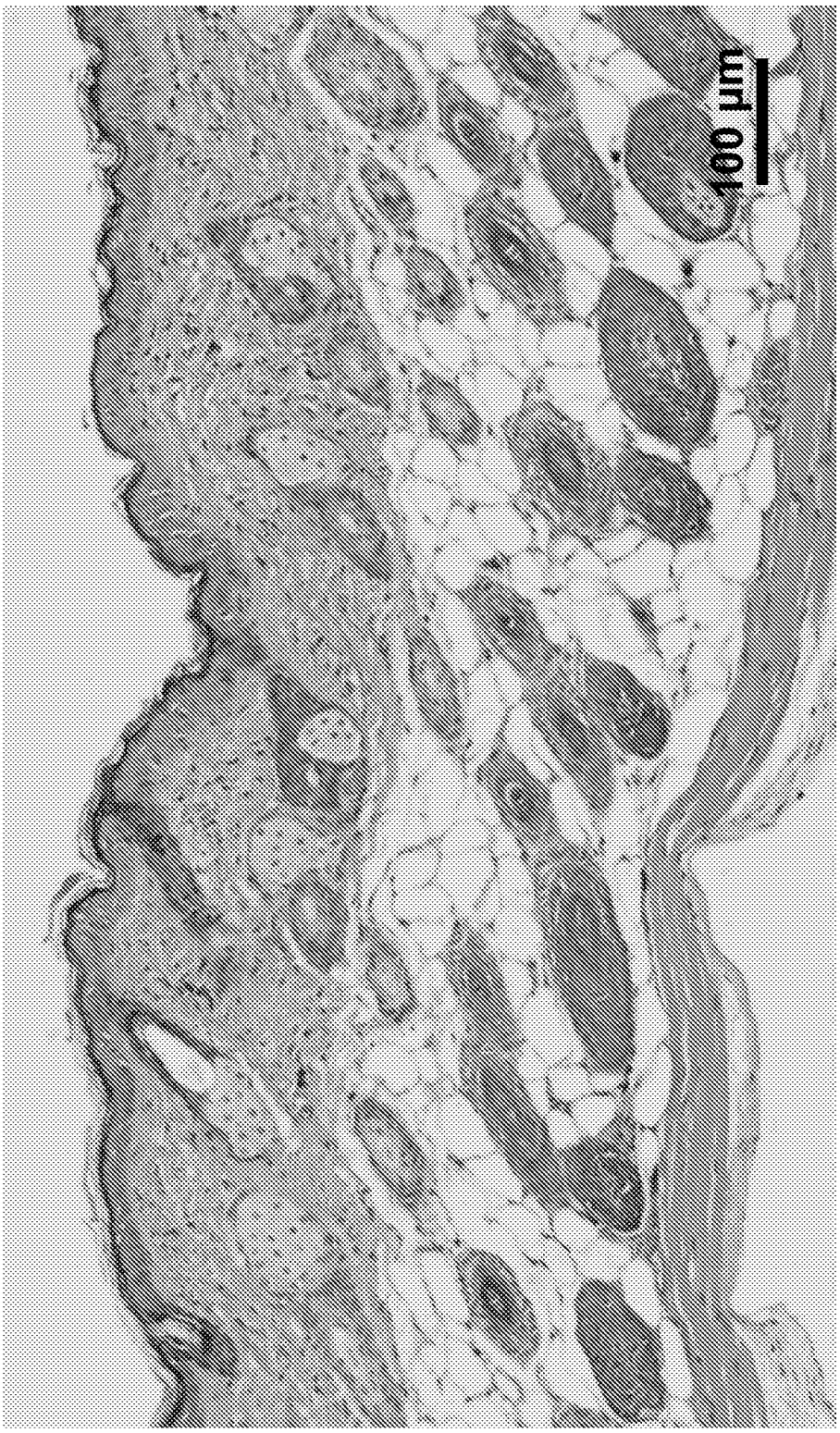


FIG. 14

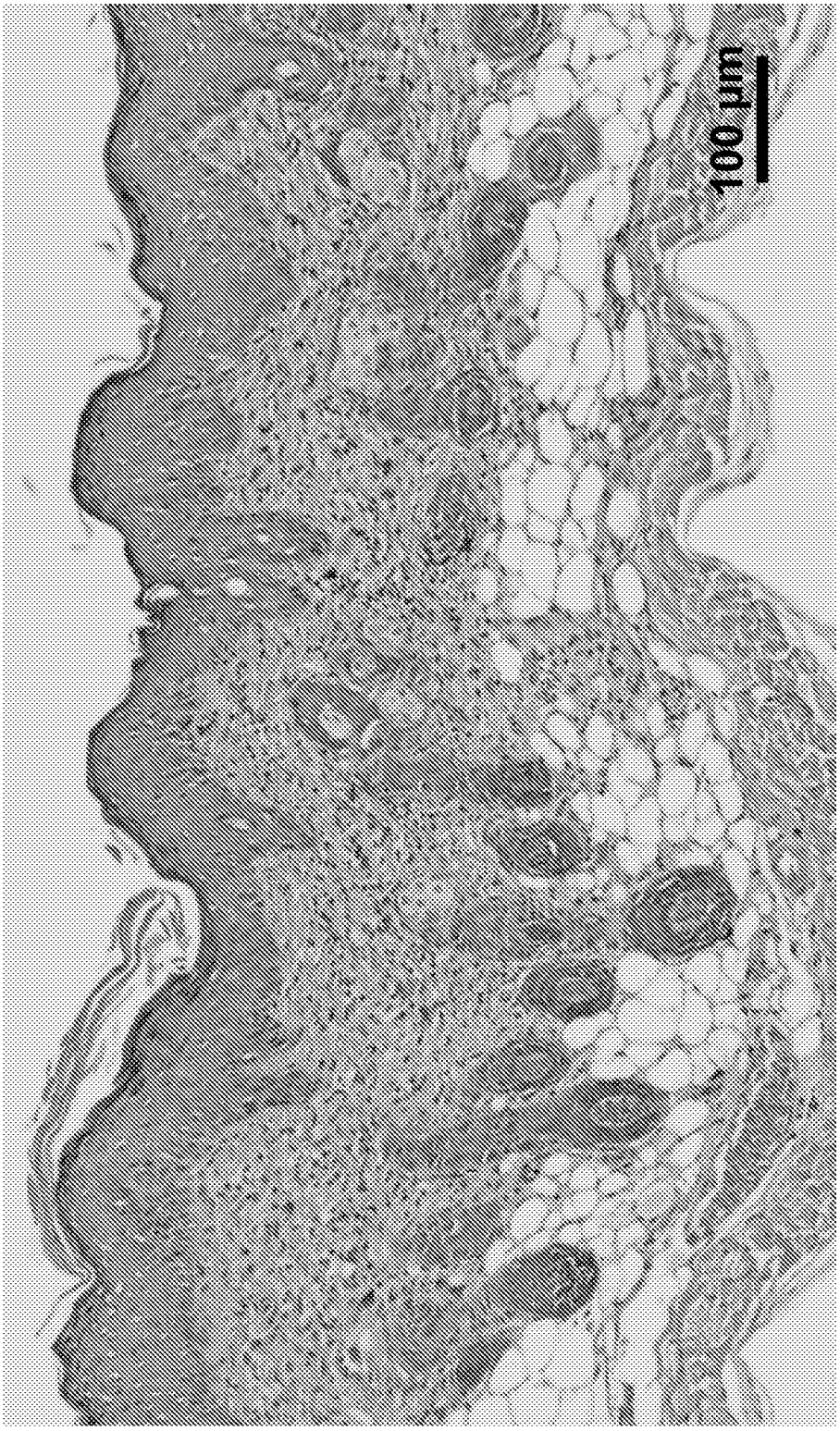


FIG. 15

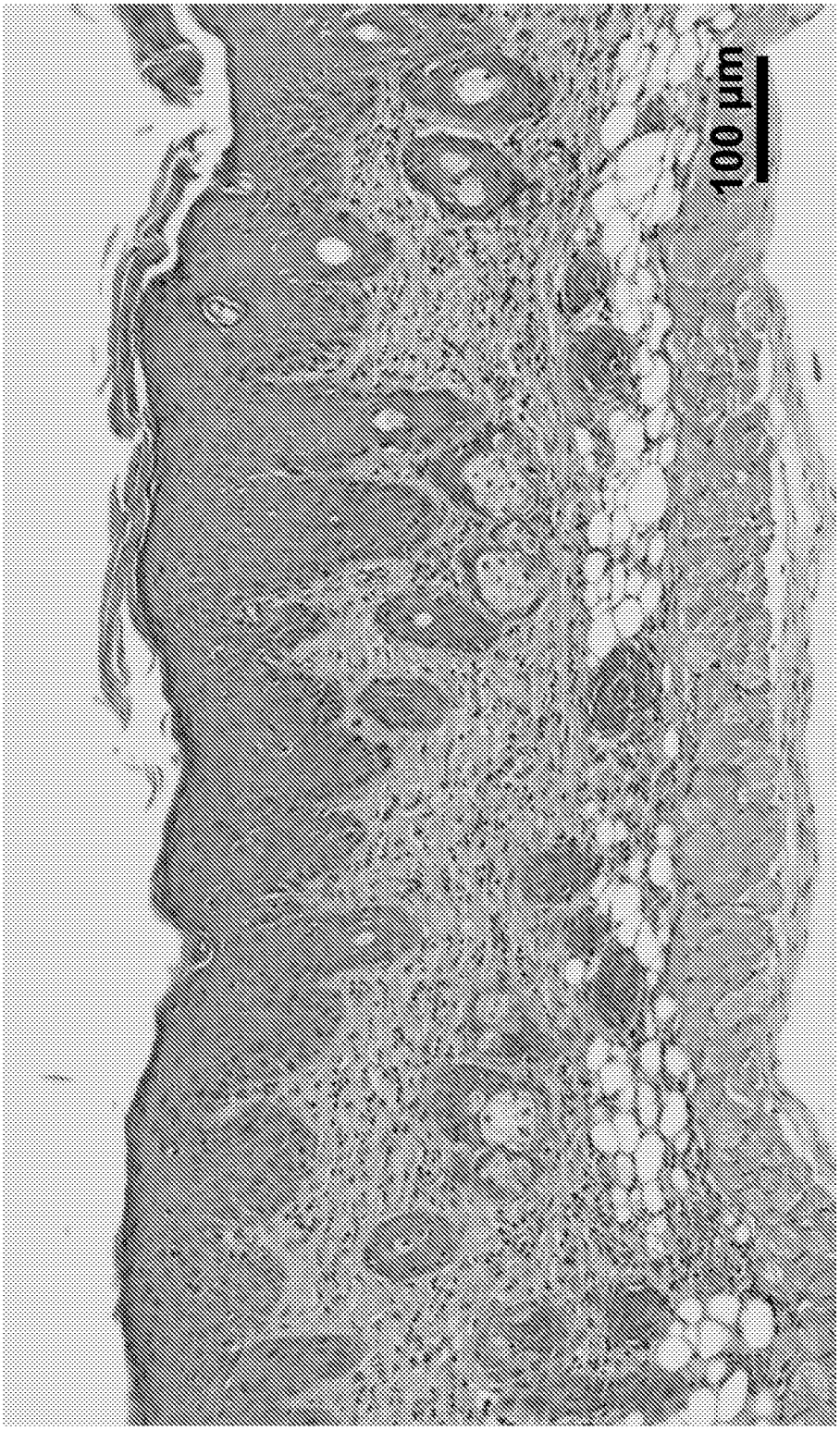


FIG. 16

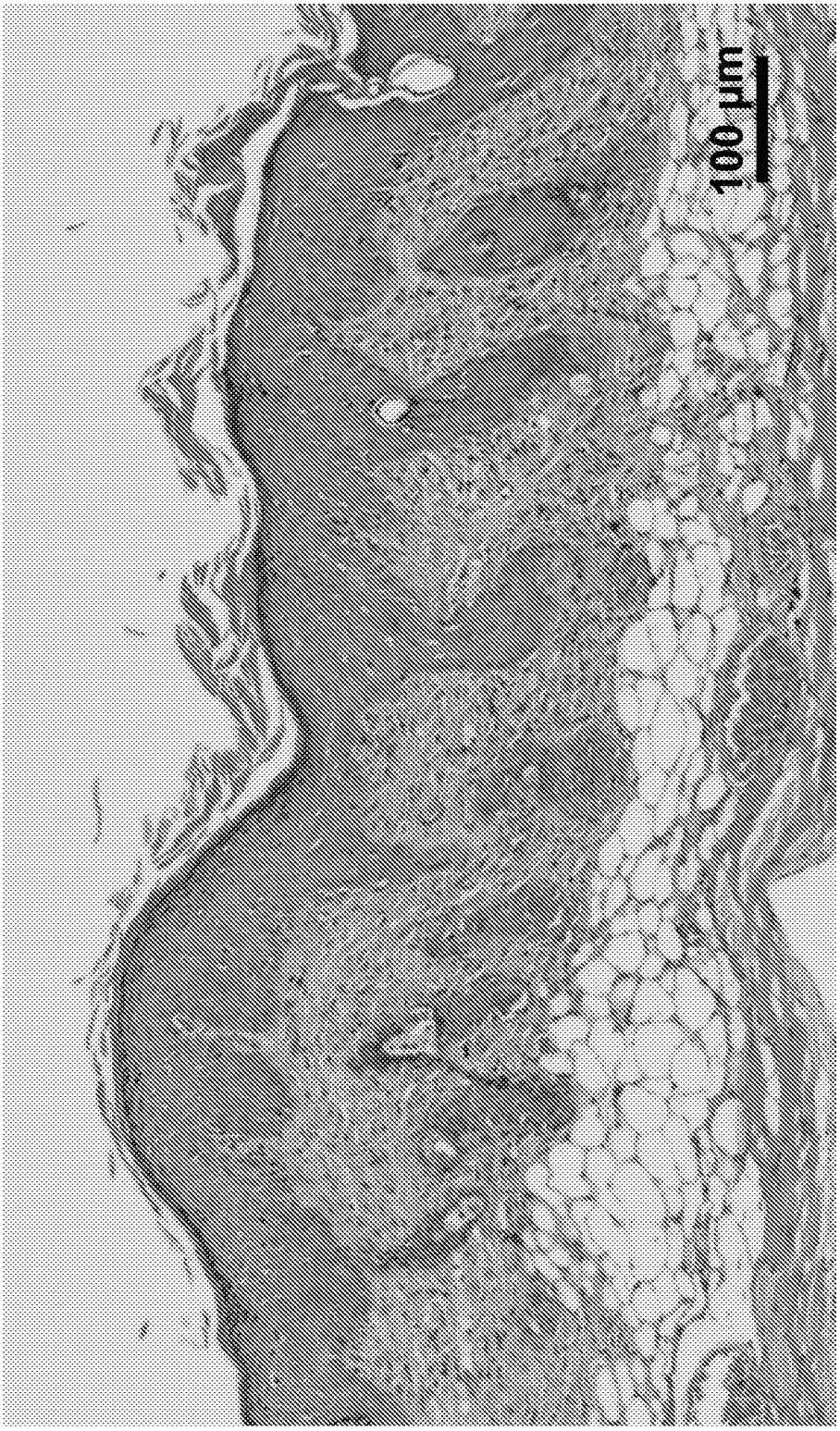


FIG. 17

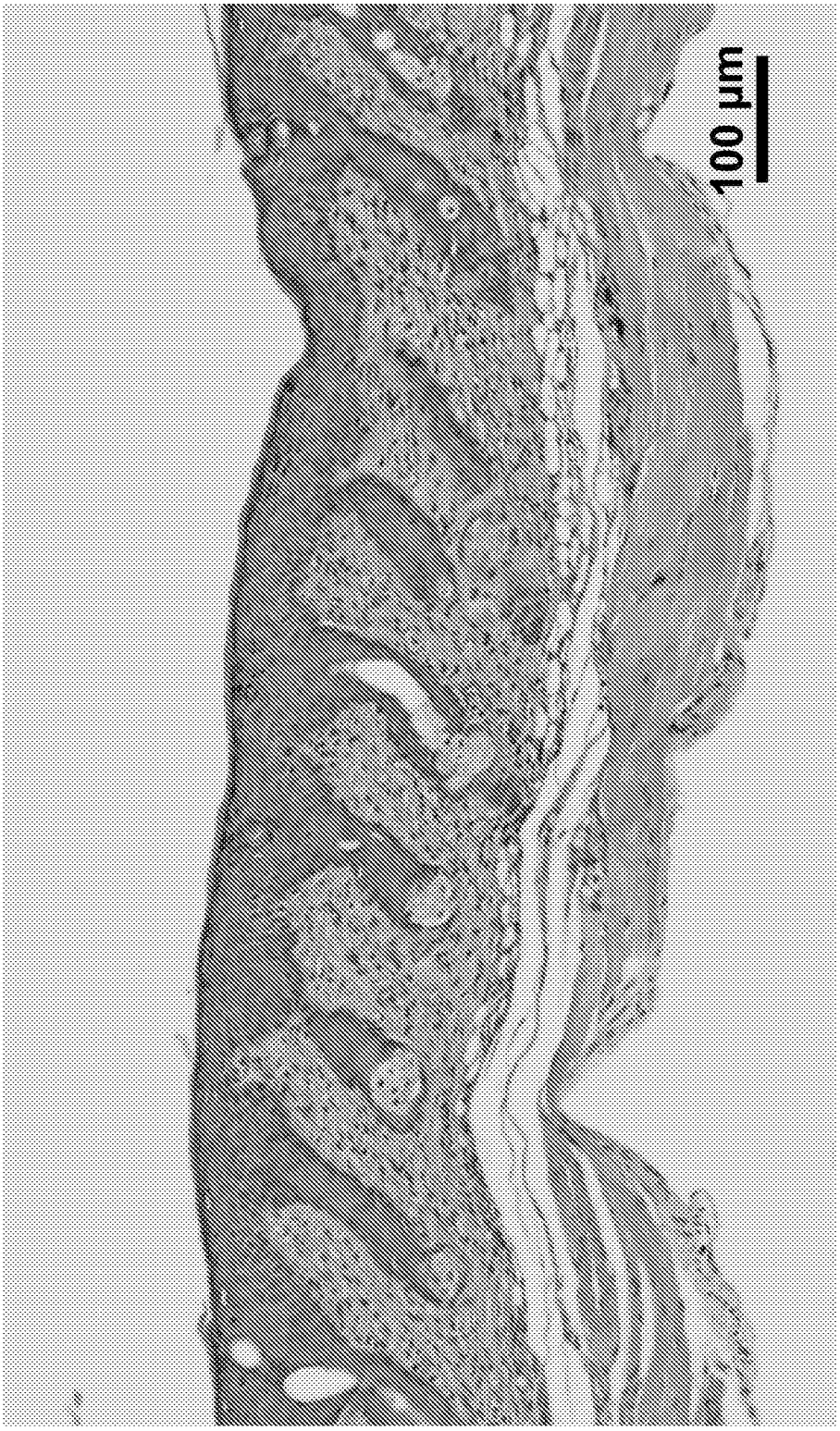


FIG. 18

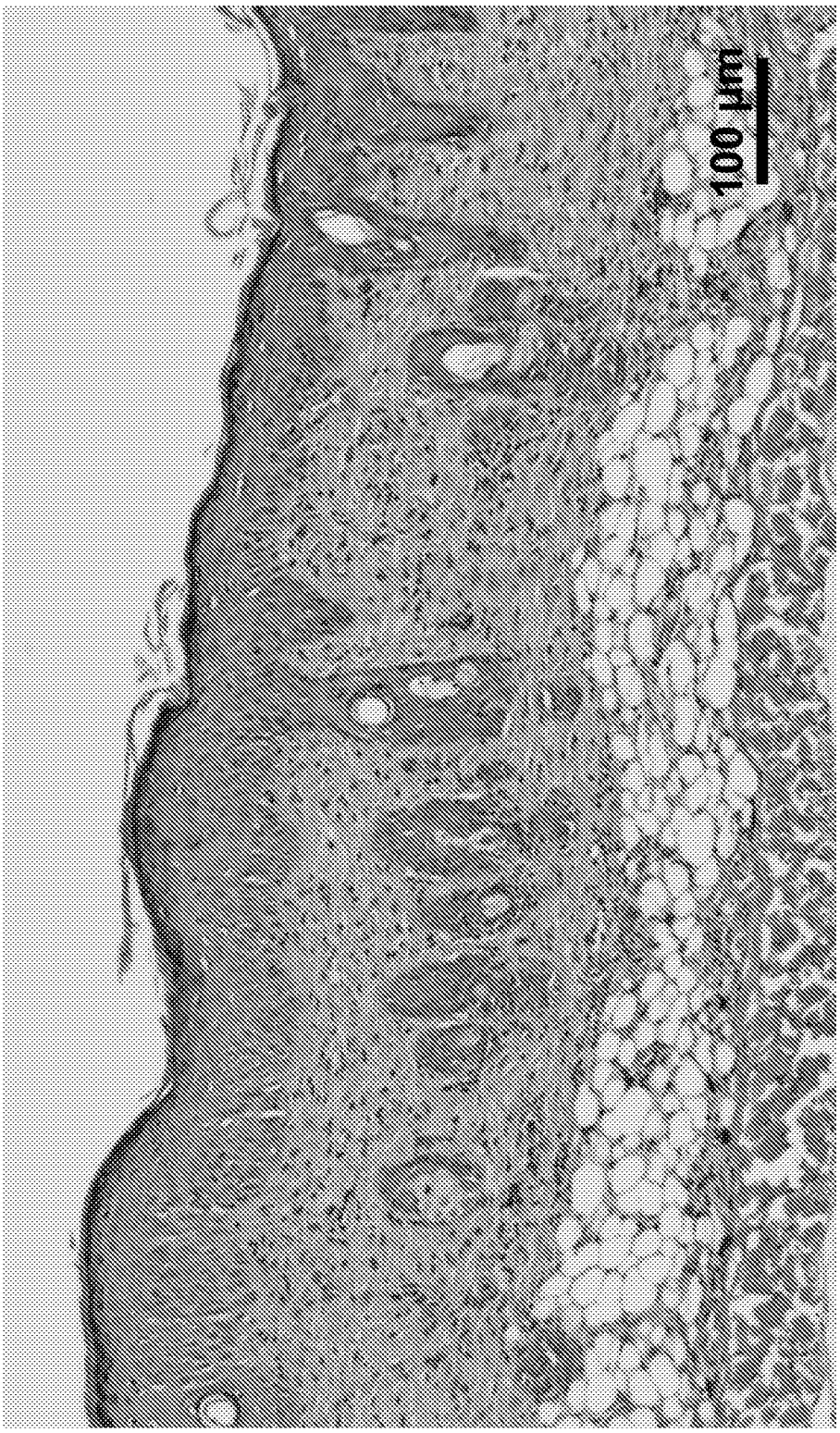


FIG. 19

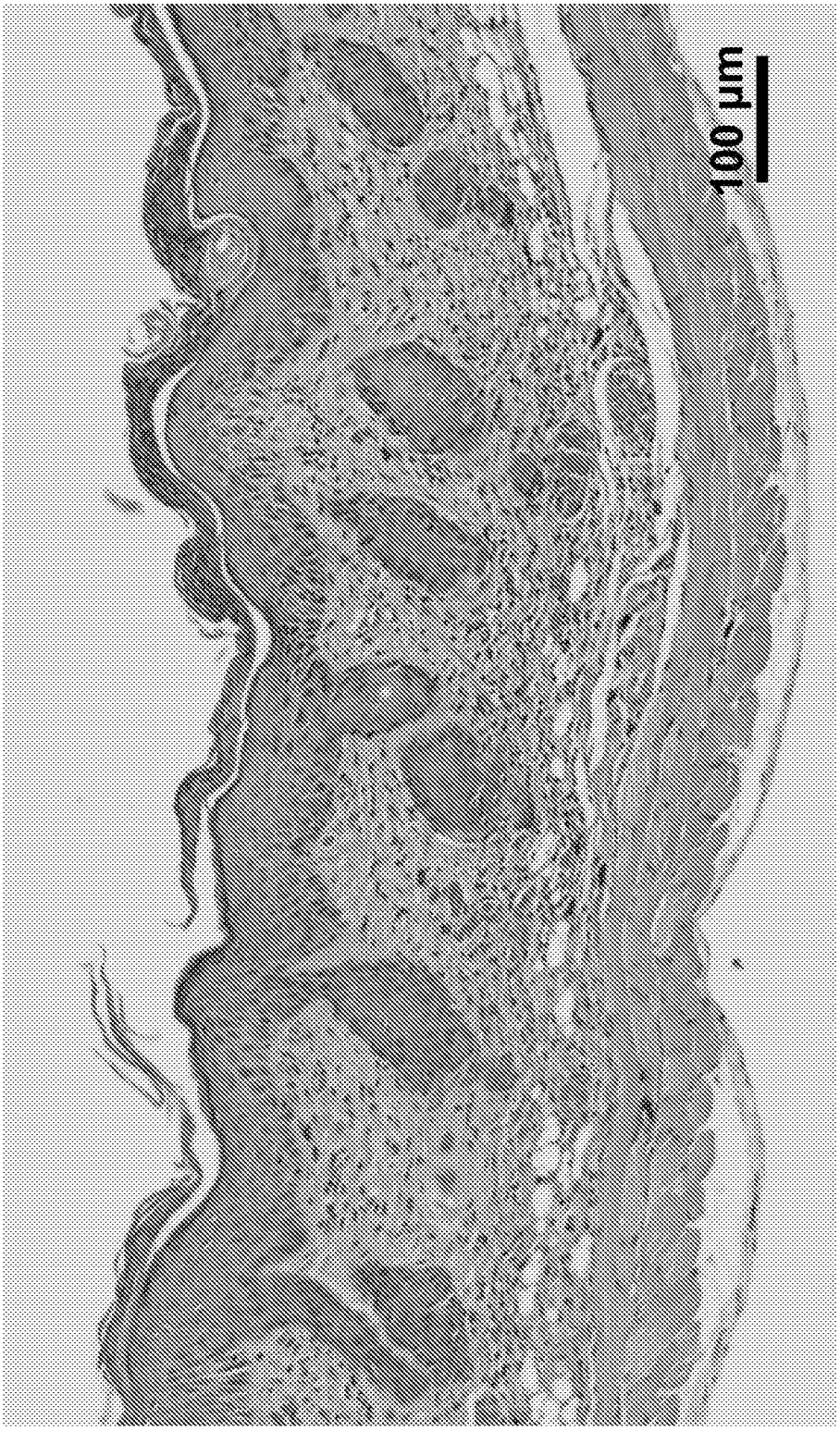


FIG. 20

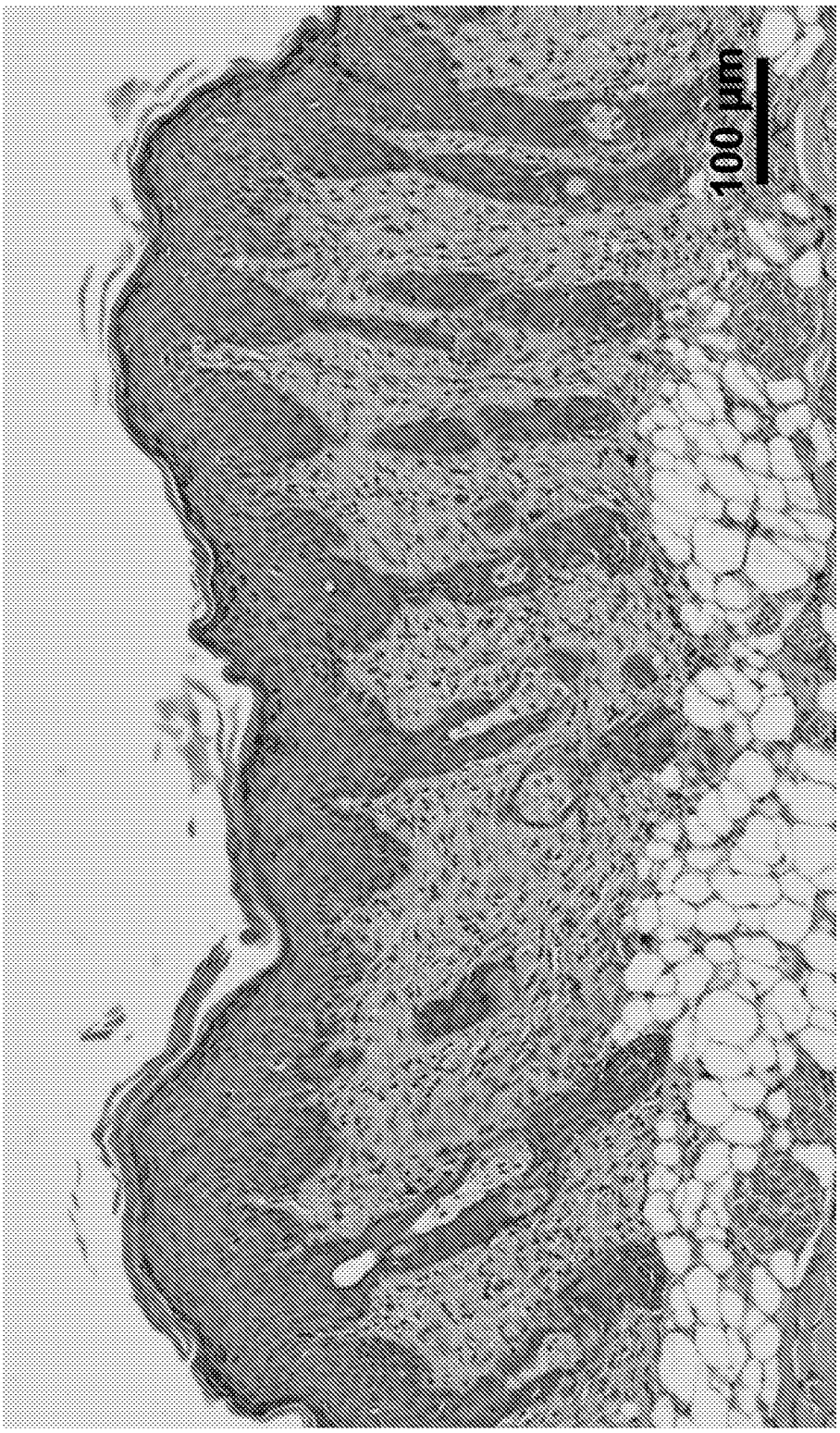


FIG. 21

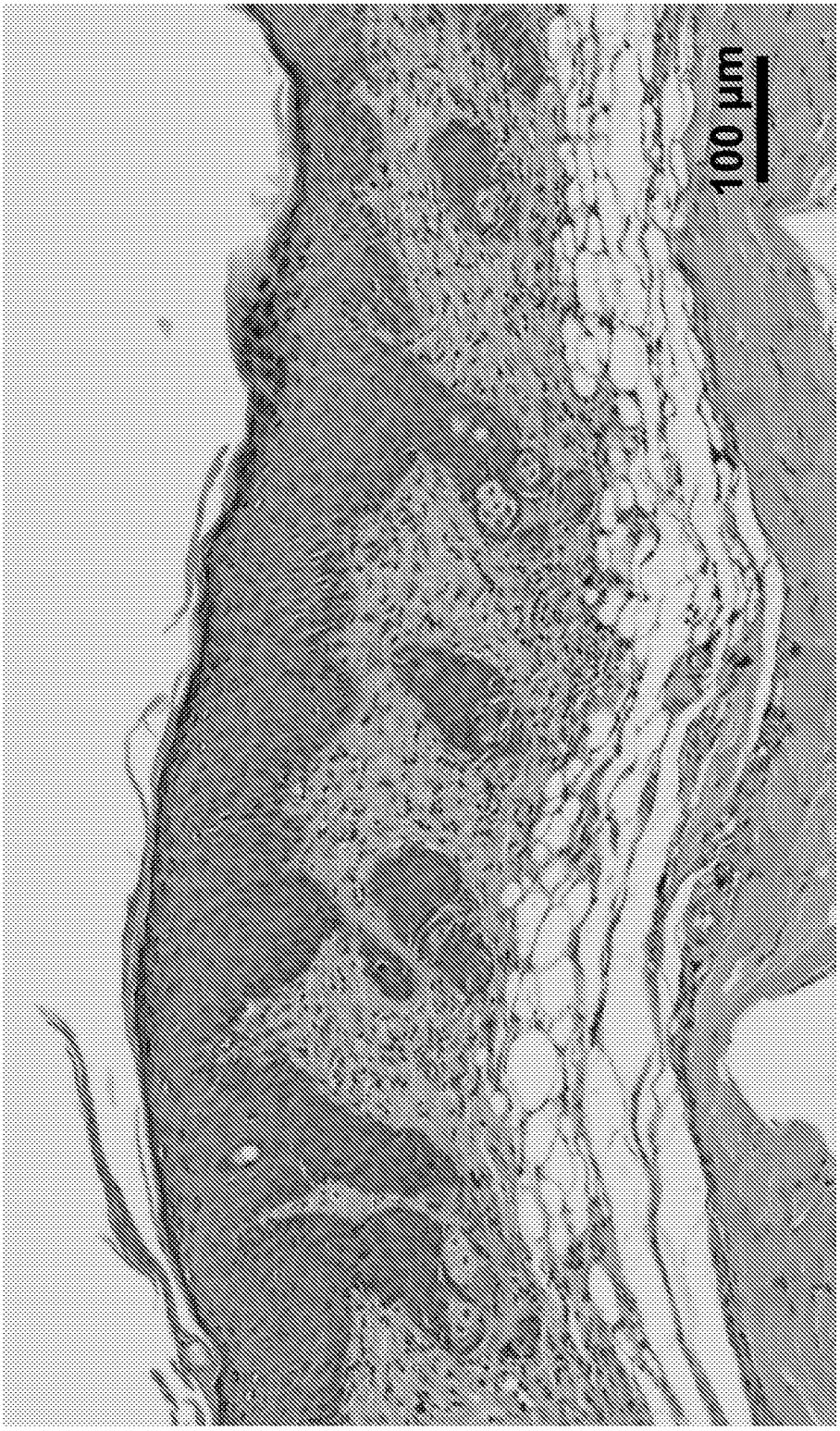


FIG. 22

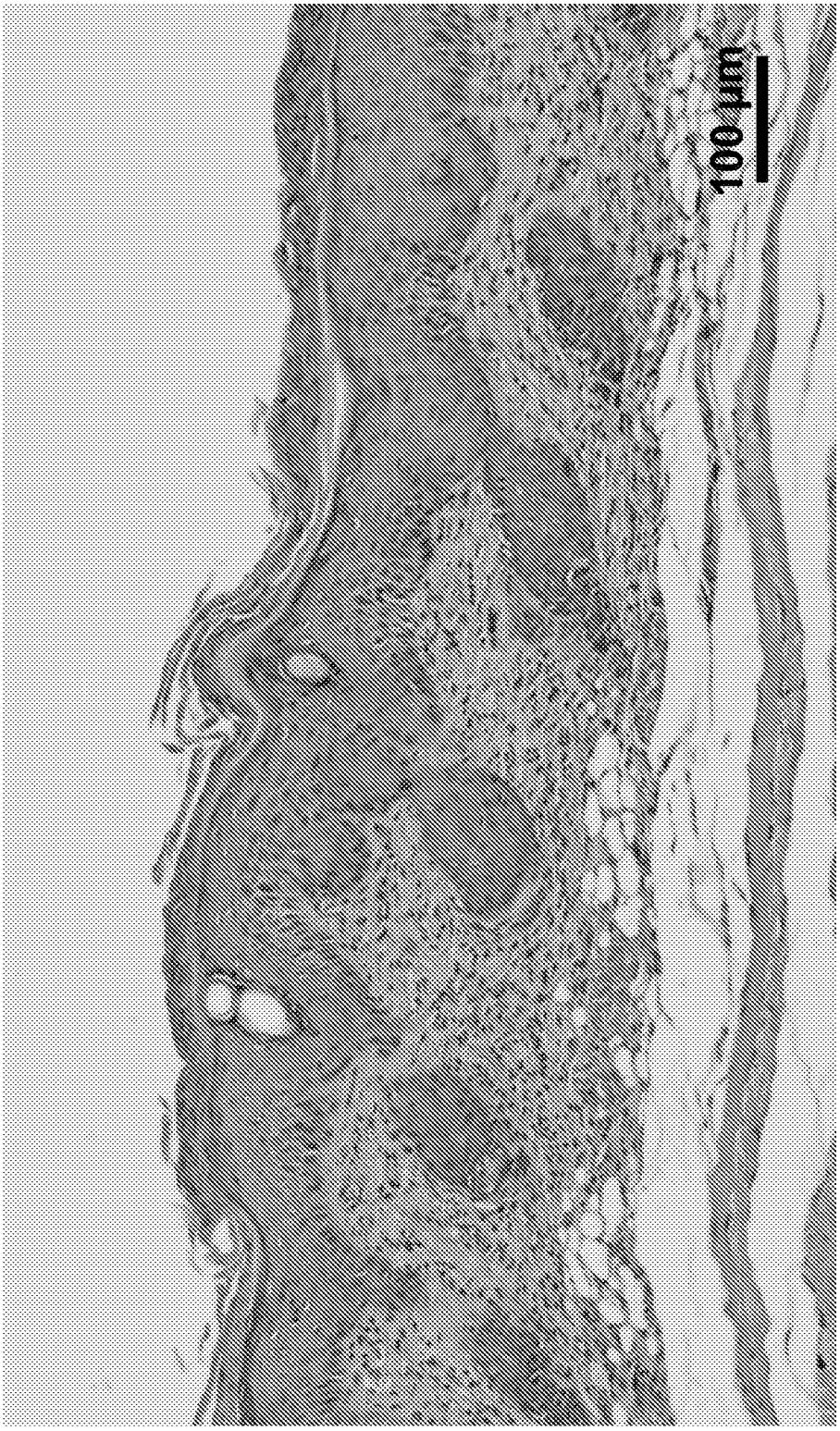
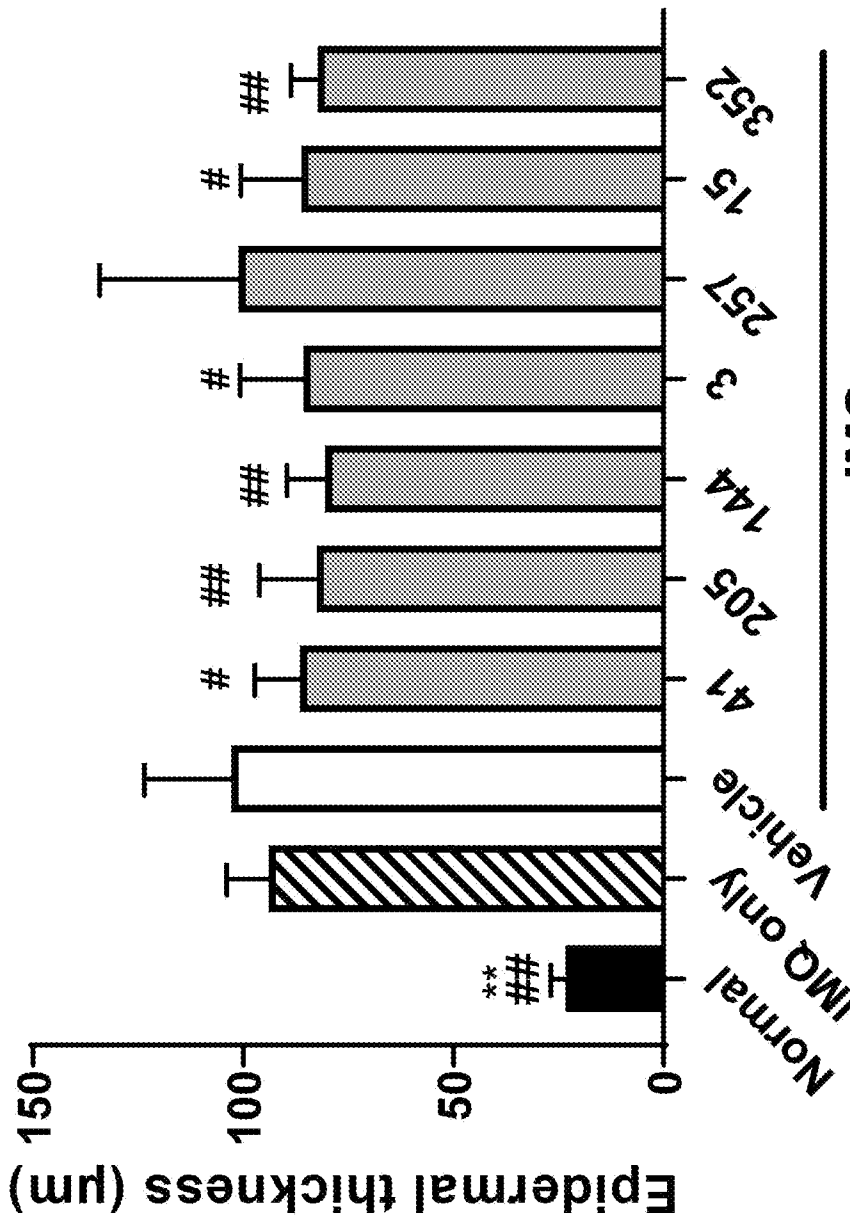


FIG. 23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100
50
0
Normal
IMQ only
Vehicle
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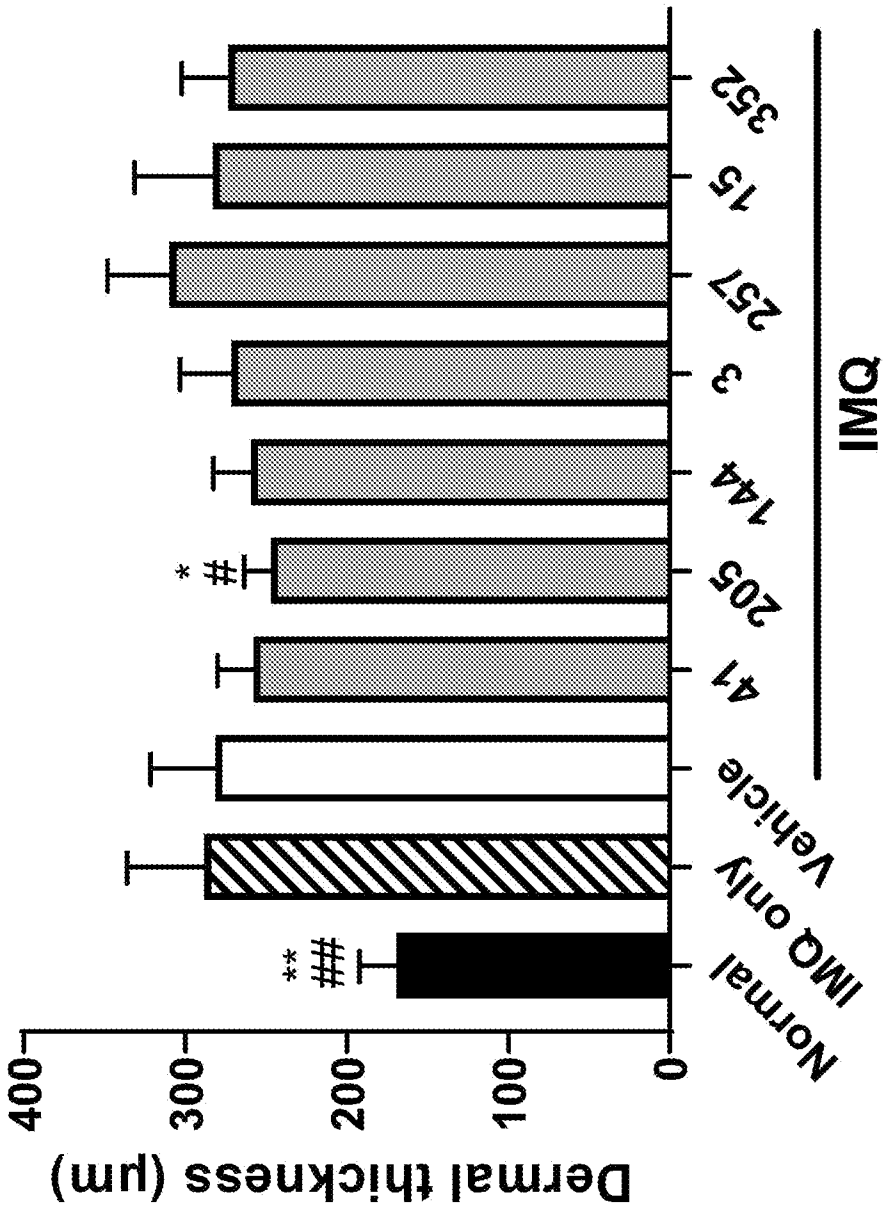
205
144
3
257
15
352
IMQ
**
##
#
##
#
##
#
##

FIG. 24


Dermal thickness (μm)
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300
200
100
0
Normal
IMQ only
Vehicle
4
205
144
3
257
15
352
IMQ
**
##
*
#

FIG. 25

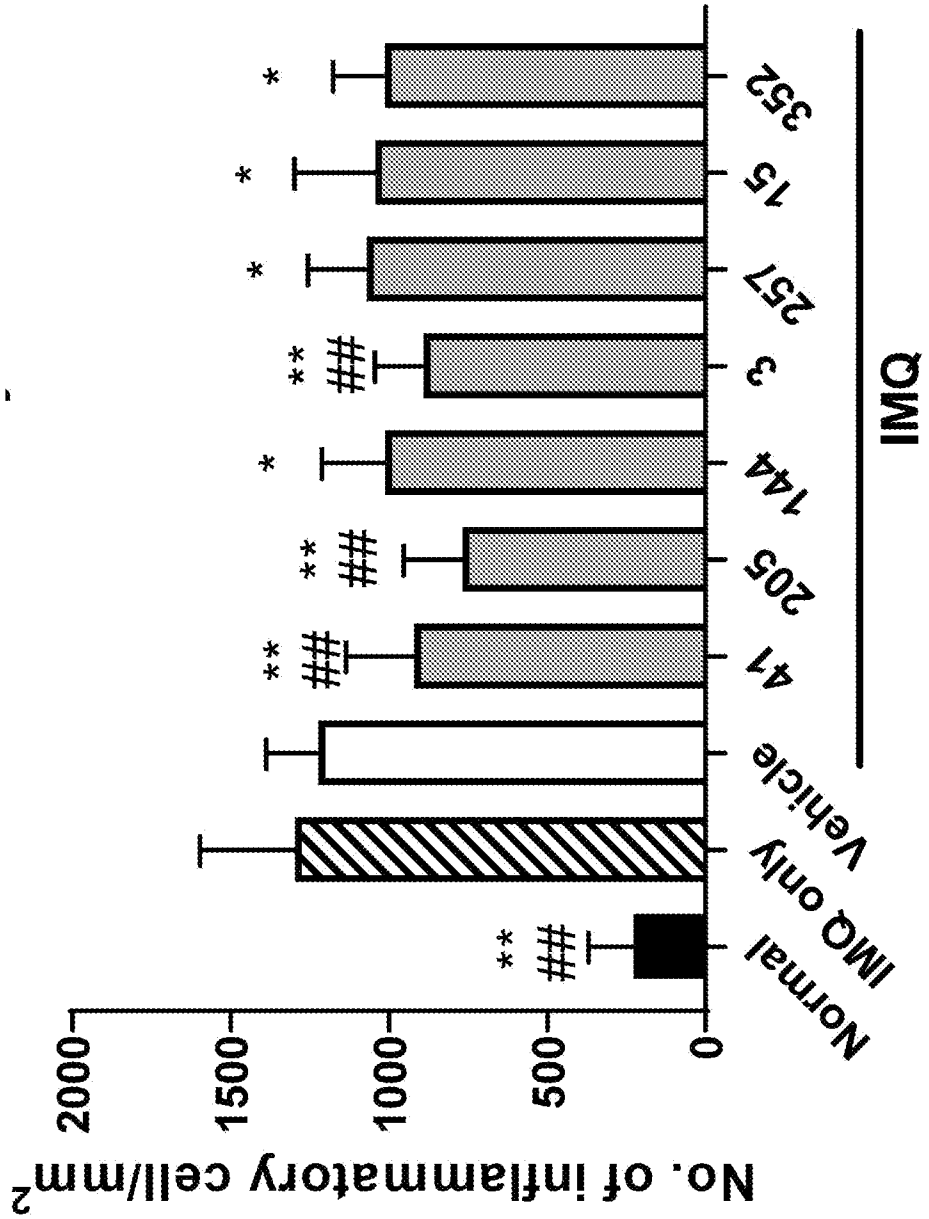
No. of inflammatory cell/mm2
2000
1500
1000
500
0
Normal
IMQ only
Vehicle
41
205
144
3
257
15
352
IMQ
**
##
*

FIG. 26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/000612

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/519(2006.01)i; **A61K 31/5377**(2006.01)i; **A61P 29/00**(2006.01)i; **A61P 17/00**(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/519(2006.01); A61K 31/166(2006.01); A61K 31/4162(2006.01); A61K 31/4439(2006.01); A61K 31/5377(2006.01); C07D 487/04(2006.01); G01N 33/15(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN(registry, caplus), google & Keywords: CFTR(cystic fibrosis transmembrane conductance regulator) modulator, PDE4(Phosphodiesterase-4) inhibitor, inflammatory disease, pyrazolo[1,5-a]pyrimidine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004-087153 A2 (CHIRON CORPORATION) 14 October 2004 (2004-10-14) claims 1, 22, 27; paragraphs [0086], [00200]; table 1	5-8
A	JP 2004-170323 A (SUMITOMO PHARMACEUT CO., LTD.) 17 June 2004 (2004-06-17) the whole document	5-8
A	JP 2018-076234 A (TAISHO PHARMACEUTICAL CO., LTD.) 17 May 2018 (2018-05-17) the whole document	5-8
A	WO 2010-074284 A1 (AJINOMOTO CO., INC.) 01 July 2010 (2010-07-01) the whole document	5-8
A	WO 2008-045664 A2 (KALYPSYS, INC.) 17 April 2008 (2008-04-17) the whole document	5-8

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2023	**29 March 2023**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office **189 Cheongsa-ro, Seo-gu, Daejeon** **35208, Republic of Korea**	**HEO, Joo Hyung**
Facsimile No. **+82-42-481-8578**	Telephone No. **+82-42-481-5373**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/000612

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **1-4, 9-17**
because they relate to subject matter not required to be searched by this Authority, namely:

*Claims 1-4, 9-17 pertain to methods for treatment of the human body by surgery or therapy and thus relate to a subject matter which this International Searching Authority is not required to search under PCT Article 17(2)(a)(i) and Rule 39.1(iv).

2. ☑ Claims Nos.: **10, 11, 13, 14**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

*Claims 10, 11, 13, 14 are regarded to be unclear because they refer to claims which do not comply with PCT Rule 6.4(a).

3. ☑ Claims Nos.: **9, 12, 15-17**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2022/000612

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2004-087153	A2	14 October 2004	CA	2520124	A1	14 October 2004
				EP	1608369	A2	28 December 2005
				EP	1608369	B1	26 June 2013
				EP	2258365	A1	08 December 2010
				EP	2258365	B1	29 May 2013
				ES	2423800	T3	24 September 2013
				US	2005-0136065	A1	23 June 2005
				US	7893096	B2	22 February 2011
				WO	2004-087153	A3	17 March 2005
JP	2004-170323	A	17 June 2004		None		
JP	2018-076234	A	17 May 2018	WO	2016-148145	A1	22 September 2016
WO	2010-074284	A1	01 July 2010	JP	2012-074284	A1	21 June 2012
				JP	5578490	B2	27 August 2014
				US	2011-0294781	A1	01 December 2011
				US	8314098	B2	20 November 2012
WO	2008-045664	A2	17 April 2008	US	2009-0275586	A1	05 November 2009
				WO	2008-045664	A3	07 May 2009