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(54) Title: NLRP3 MODULATORS

(57) Abstract: This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that modulate (e.g., agonize or partially agonize) NLRP3 and TLR7 and/or TLR8 that are useful, e.g., for treating a condition, disease or disorder in which a decrease in NLRP3 and TLR7 and/or TLR8 activities (e.g., a condition, disease or disorder associated with repressed or impaired NLRP3 and TLR7 and/or TLR8 signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also features compositions as well as other methods of using and making the same.



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NLRP3 MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of United States Provisional Application No. 62/324,614, filed on April 19, 2016, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that modulate (e.g., agonize or partially agonize) NLRP3 and TLR7 and/or TLR8 that are useful, e.g., for treating a condition, disease or disorder in which a decrease in NLRP3 and TLR7 and/or TLR8 activities (e.g., a condition, disease or disorder associated with repressed or impaired NLRP3 and TLR7 and/or TLR8 signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also features compositions as well as other methods of using and making the same.

BACKGROUND

Nucleotide-binding oligomerization domain-like receptors (“NLRs”) include a family of intracellular receptors that detects pathogen-associated molecular patterns (“PAMPs”) and endogenous molecules (see, e.g., .P.-Y. Ting, et al., “The NLR gene family: a standard nomenclature,” *Immunity*, vol. 28, no. 3, pp. 285–287, 2008).

NLRPs represent a subfamily of NLRs that include a Pyrin domain and are constituted by proteins such as NLRP1, NLRP3, NLRP4, NLRP6, NLRP7, and NLRP12. NLRPs are believed to be involved with the formation of multiprotein complexes termed inflammasomes (see, e.g., C. Chaput, et al., “NOD-like receptors in lung diseases,” *Frontiers in Immunology*, vol. 4, article 393, 2013). These complexes typically include one or two NLR proteins, the adapter molecule apoptosis associated speck-like containing a CARD domain (ASC) and pro-caspase-1 F (see, e.g., Bauernfeind and V. Hornung, “Of

inflammasomes and pathogens—sensing of microbes by the inflammasome,” *EMBO Molecular Medicine*, vol. 5, no. 6, pp. 814–826, 2013).

One such inflammasome is formed by the NLRP3 scaffold, the ASC adaptor and caspase-1 (see, e.g., J. A. Hirota, et al., “The airway epithelium nucleotide-binding domain and leucine-rich repeat protein 3 inflammasome is activated by urban particulate matter,” *Journal of Allergy and Clinical Immunology*, vol. 129, no. 4, pp. 1116.e6–1125.e6, 2012), and its expression is believed to be induced by inflammatory cytokines and TLR agonists in myeloid cells and human bronchial epithelial cells (*Id.*). The NLRP3 inflammasome is believed to mediate the caspase-1-dependent conversion of pro-IL-1 β and pro-IL-18 to IL-1 β and IL-18. Further, IL-1 β and IL-18 have been shown to play an important role in the treatment of various types of cancer (see, e.g., *EMBO Mol Med.* **2012** 4:1276 and *PLoS One* **2011** 6:e24241). IL-18 has been shown to override resistance to checkpoint inhibitors in colon cancer tumor models (*Clin. Cancer Res.* **2016** Jan 11. pii: clincanres.1655.2015).

Toll-Like Receptors (“TLRs”) are a family of receptors, which have been shown to recognize a structural diversity of PAMPs like glycans, lipids, proteins, lipoproteins, and nucleic acids and are and are believed to play a key role in the inflammatory and innate immune response. TLRs are expressed in various cellular compartments. TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11 are predominantly expressed on the cell surface, while TLR3, TLR7, TLR8, TLR9, and TLR13 are expressed in intracellular vesicles such as the endoplasmic reticulum, endosomes, lysosomes, and endolysosomes and mainly recognize nucleic acid. TLRs are expressed in a broad variety of cells such as dendritic cells, macrophages, neutrophils, monocytes, T and B cells, epithelial cells, endothelial cells, fibroblasts, and even neural cells. It has also been reported that plasmacytoid dendritic cells and mast cells express TLR7 and TLR8, respectively. See, e.g., Javier Oviedo-Boyso, et al., “Collaborative Action of Toll-Like and Nod-Like Receptors as Modulators of the Inflammatory Response to Pathogenic Bacteria,” *Mediators of Inflammation*, vol. 2014, Article ID 432785, 16 pages, 2014. doi:10.1155/2014/432785

SUMMARY

This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that modulate (e.g., agonize or partially agonize) NLRP3 and TLR7 and/or TLR8 that are useful, e.g., for treating a condition, disease or disorder in which a decrease in NLRP3 and TLR7 and/or TLR8 activities (e.g., a condition, disease or disorder associated with repressed or impaired NLRP3 and TLR7 and/or TLR8 signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also features compositions as well as other methods of using and making the same.

An "agonist" of NLRP3 includes compounds that, at the protein level, directly bind or modify NLRP3 such that an activity of NLRP3 is increased, e.g., by activation, stabilization, altered distribution, or otherwise.

Certain compounds described herein that agonize NLRP3 to a lesser extent than a NLRP3 full agonist can function in assays as antagonists as well as agonists. These compounds antagonize activation of NLRP3 by a NLRP3 full agonist because they prevent the full effect of NLRP3 interaction. However, the compounds also, on their own, activate some NLRP3 activity, typically less than a corresponding amount of the NLRP3 full agonist. Such compounds may be referred to as "partial agonists of NLRP3".

In some embodiments, the compounds described herein are agonists (e.g. full agonists) of NLRP3. In other embodiments, the compounds described herein are partial agonists of NLRP3.

An "agonist" of TLR7 includes compounds that, at the protein level, directly bind or modify TLR7 such that an activity of TLR7 is increased, e.g., by activation, stabilization, altered distribution, or otherwise.

Certain compounds described herein that agonize TLR7 to a lesser extent than a TLR7 full agonist can function in assays as antagonists as well as agonists. These compounds antagonize activation of TLR7 by a TLR7 full agonist because they prevent the full effect of TLR7 interaction. However, the compounds also, on their own, activate

some TLR7 activity, typically less than a corresponding amount of the TLR7 full agonist. Such compounds may be referred to as "partial agonists of TLR7".

In some embodiments, the compounds described herein are agonists (e.g. full agonists) of TLR7. In other embodiments, the compounds described herein are partial
5 agonists of TLR7.

An "agonist" of TLR8 includes compounds that, at the protein level, directly bind or modify TLR8 such that an activity of TLR8 is increased, e.g., by activation, stabilization, altered distribution, or otherwise.

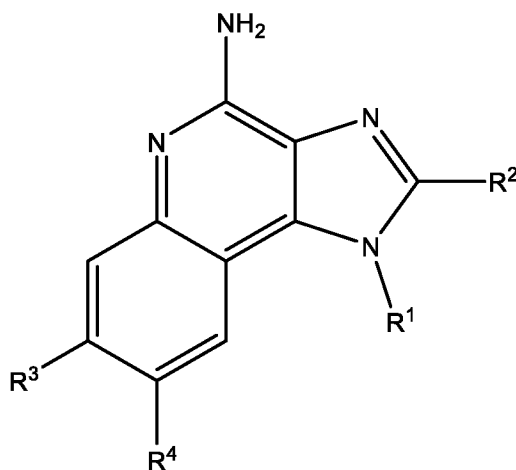
Certain compounds described herein that agonize TLR8 to a lesser extent than a
10 TLR8 full agonist can function in assays as antagonists as well as agonists. These compounds antagonize activation of TLR8 by a TLR8 full agonist because they prevent the full effect of TLR8 interaction. However, the compounds also, on their own, activate some TLR8 activity, typically less than a corresponding amount of the TLR8 full agonist. Such compounds may be referred to as "partial agonists of TLR8".

In some embodiments, the compounds described herein are agonists (e.g. full
15 agonists) of TLR8. In other embodiments, the compounds described herein are partial agonists of TLR8.

In some embodiments, the compounds described herein are full agonists of NLRP3 and TLR7 and/or TLR8. In some embodiments, the compounds described herein are partial
20 agonists of NLRP3 and TLR7 and/or TLR8. This disclosure also contemplates chemical entities that are full agonists of at least one of NLRP3 and TLR7 and/or TLR8 and partial agonists at least one of NLRP3 and TLR7 and/or TLR8.

Generally, a receptor exists in an active (Ra) and an inactive (Ri) conformation. Certain compounds that affect the receptor can alter the ratio of Ra to Ri (Ra/Ri). For
25 example, a full agonist increases the ratio of Ra/Ri and can cause a "maximal", saturating effect. A partial agonist, when bound to the receptor, gives a response that is lower than that elicited by a full agonist (e.g., an endogenous agonist). Thus, the Ra/Ri for a partial agonist is less than for a full agonist. However, the potency of a partial agonist may be greater or less than that of the full agonist.

In one aspect, compounds of Formula I, or a pharmaceutically acceptable salt thereof, are featured:



5 in which **R¹**, **R²**, **R³**, and **R⁴** can be as defined anywhere herein.

In one aspect, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients.

10

In one aspect, methods for modulating (e.g., agonizing, partially agonizing, antagonizing) NLRP3 and TLR7 and/or TLR8 activities are featured that include contacting NLRP3 and TLR7 and/or TLR8 with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells, each independently comprising one or more of NLRP3 and TLR7 and/or TLR8 (e.g., THP-1 cells, HEK blue cells, innate immune cells, e.g., mast cells, macrophages, dendritic cells (DCs), and natural killer cells) with the chemical entity. The contacting can, in some cases, induce an immune response sufficient to kill at least one of the one or more cancer cells. Methods can also include *in vivo* methods; e.g., administering the chemical entity to a subject (e.g., a human) having a

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disease in which repressed or impaired NLRP3 and TLR7 and/or TLR8 signaling contributes to the pathology and/or symptoms and/or progression of the disease (e.g., cancer; e.g., a refractory cancer).

5 In another aspect, methods of treating cancer are featured that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

10 In a further aspect, methods of inducing an immune response (e.g., an innate immune response) in a subject in need thereof are featured that include administering to the subject an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

15 In a further aspect, methods of treatment of a disease in which repressed or impaired NLRP3 and TLR7 and/or TLR8 signaling contributes to the pathology and/or symptoms and/or progression of the disease are featured that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

20 In another aspect, methods of treatment are featured that include administering to a subject having a disease in which repressed or impaired NLRP3 and TLR7 and/or TLR8 signaling contributes to the pathology and/or symptoms and/or progression of the disease an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

25 In a further aspect, methods of treatment that include administering to a subject a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same), wherein the chemical entity is administered in an amount effective to treat a disease in which repressed or impaired NLRP3 and TLR7 and/or TLR8 signaling contributes to the pathology and/or symptoms and/or progression of the disease, thereby treating the disease.

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Embodiments can include one or more of the following features.

The chemical entity can be administered in combination with one or more additional cancer therapies (e.g., surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy, or a combination thereof; e.g., chemotherapy that includes administering one or more (e.g., two, three, four, five, six, or more) additional chemotherapeutic agents. Non-limiting examples of additional chemotherapeutic agents is selected from an alkylating agent (e.g., cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin); an anti-metabolite (e.g., azathioprine and/or mercaptopurine); a terpenoid (e.g., a vinca alkaloid and/or a taxane; e.g., Vincristine, Vinblastine, Vinorelbine and/or Vindesine Taxol, Paclitaxel and/or Docetaxel); a topoisomerase (e.g., a type I topoisomerase and/or a type 2 topoisomerase; e.g., camptothecins, such as irinotecan and/or topotecan; amsacrine, etoposide, etoposide phosphate and/or teniposide); a cytotoxic antibiotic (e.g., actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and/or mitomycin); a hormone (e.g., a lutenizing hormone releasing hormone agonist; e.g., leuprolidine, goserelin, triptorelin, histrelin, bicalutamide, flutamide and/or nilutamide); an antibody (e.g., Abciximab, Adalimumab, Alemtuzumab, Atlizumab, Basiliximab, Belimumab, Bevacizumab, Bretuximab vedotin, Canakinumab, Cetuximab, Ceertolizumab pegol, Daclizumab, Denosumab, Eculizumab, Efalizumab, Gemtuzumab, Golimumab, Golimumab, Ibritumomab tiuxetan, Infliximab, Ipilimumab, Muromonab-CD3, Natalizumab, Ofatumumab, Omalizumab, Palivizumab, Panitumuab, Ranibizumab, Rituximab, Tocilizumab, Tositumomab and/or Trastuzumab); an anti-angiogenic agent; a cytokine; a thrombotic agent; a growth inhibitory agent; an anti-helminthic agent; and an immune checkpoint inhibitor that targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70–CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–

LIGHT-LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM – LIGHT, HVEM-BTLA-CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS-ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2-TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, 5 ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA-CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or PD-L1) and other immunomodulatory agents, such as interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming growth factor- β (TGF β), CD39, CD73 10 Adenosine-CD39-CD73, and CXCR4-CXCL12.

The subject can have cancer; e.g., the subject has undergone and/or is undergoing and/or will undergo one or more cancer therapies.

Non-limiting examples of cancer include acute myeloid leukemia, adrenocortical carcinoma, Kaposi sarcoma, lymphoma, anal cancer, appendix cancer, teratoid/rhabdoid 15 tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain cancer, breast cancer, bronchial tumor, carcinoid tumor, cardiac tumor, cervical cancer, chordoma, chronic lymphocytic leukemia, chronic myeloproliferative neoplasm, colon cancer, colorectal cancer, craniopharyngioma, bile duct cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, eye cancer, fallopian tube 20 cancer, gallbladder cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, germ cell tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hypopharyngeal cancer, pancreatic cancer, kidney cancer, laryngeal cancer, chronic myelogenous leukemia, lip and oral cavity cancer, lung cancer, melanoma, Merkel cell carcinoma, mesothelioma, mouth cancer, oral cancer, osteosarcoma, ovarian cancer, penile 25 cancer, pharyngeal cancer, prostate cancer, rectal cancer, salivary gland cancer, skin cancer, small intestine cancer, soft tissue sarcoma, testicular cancer, throat cancer, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, and vulvar cancer.

In other embodiments, the mammal has been identified as having a cancer or an infectious disease. Representative infectious diseases include, without limitation, *Acinobacter* infection, actinomycosis, African sleeping sickness, acquired immunodeficiency syndrome, amebiasis, anaplasmosis, anthrax, *Arcanobacterium*
5 *haemolyticum* infection, Argentine hemorrhagic fever, ascariasis, aspergillosis, astrovirus infection, babesiosis, *Bacillus cereus* infection, bacterial pneumonia, bacterial vaginosis, *Bacteroides* infection, balantidiasis, *Baylisascaris* infection, BK virus infection, black piedra, *Blastocystis hominis* infection, blastomycosis, Bolivian hemorrhagic fever, botulism, Brazilian hemorrhagic fever, brucellosis, bubonic plague, *Burkholderi* infection,
10 Buruli ulcer, *Calicivirus* infection, campylobacteriosis, candidiasis, cat-scratch disease, cellulitis, Chagas disease, chancroid, chickenpox, chikungunya, chlamydia, *Chlamydophila pneumoniae* infection, cholera, chromoblastomycosis, clonorchiasis, *Clostridium difficile* infection, coccidioidomycosis, Colorado tick fever, common cold, Creutzfeldt-Jakob disease, Crimean-Congo hemorrhagic fever, cryptococcosis,
15 cryptosporidiosis, cutaneous larva migrans, cyclosporiasis, cysticercosis, cytomegalovirus infection, dengue fever, *Desmodermus* infection, deintamoebiasis, diphtheria, diphyllbothriasis, dracunculiasis, ebola hemorrhagic fever, echinococcosis, ehrlichiosis, enterobiasis, *Enterococcus* infection, *Enterovirus* infection, epidemic typhus, erythema infection, exanthema subitum, fasciolopsiasis, fasciolosis, fatal familial insomnia, filariasis, food poisoning by *Clostridium myonecrosis*, free-living amebic infection,
20 *Fusobacterium* infection, gas gangrene, geotrichosis, Gerstmann-Sträussler-Scheinker syndrome, giardiasis, glanders, gnathostomiasis, gonorrhea, granuloma inguinale, Group A streptococcal infection, Group B streptococcal infection, *Haemophilus influenzae* infection, hand foot and mouth disease, hantavirus pulmonary syndrome, Heartland virus disease, *Heliobacter pylori* infection, hemolytic-uremic syndrome, hemorrhagic fever with
25 renal syndrome, hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, herpes simplex, histoplasmosis, hookworm infection, human bocavirus infection, human ewingii ehrlichiosis, human granulocyte anaplasmosis, human metapneumovirus infection, human monocytic ehrlichiosis, human papillomavirus infection, human parainfluenza virus
30 infection, hymenolepiasis, Epstein-Barr virus infectious mononucleosis, influenza,

isoporiasis, Kawasaki disease, keratitis, *Kingella kingae* infection, kuru, lassa fever, Legionnaires' disease, Pontiac fever, leishmaniasis, leprosy, leptospirosis, listeriosis, Lyme disease, lymphatic filariasis, lymphocytic choriomeningitis, malaria, Marburg hemorrhagic fever, measles, Middle East respiratory syndrome, melioidosis, meningitis, meningococcal
5 disease, metagonimiasis, microsporidiosis, molluscum contagiosum, monkeypox, mumps, murine typhus, mycoplasma pneumonia, mycetoma, myiasis, neonatal conjunctivitis, variant Creutzfeldt-Jakob disease, nocardiosis, onchocerciasis, paracoccidiodomycosis, paragonimiasis, pasteurellosis, pediculosis capitis, pediculosis corporis, pediculosis pubis, pelvic inflammatory disease, pertussis, plague, pneumonia, poliomyelitis, *Prevotella*
10 infection, primary amoebic meningoencephalitis, progressive multifocal leukoencephalopathy, psittacosis, Q fever, rabies, relapsing fever, respiratory syncytial virus infection, rhinosporidiosis, rhinovirus infection, rickettsial infection, rickettsialpox, Rift Valley Fever, Rocky Mountain spotted fever, rotavirus infection, rubella, salmonellosis, severe acute respiratory syndrome, scabies, schistosomiasis, sepsis,
15 shigellosis, shingles, smallpox, sporothrichosis, staphylococcal food poisoning, staphylococcal infection, staphylococcal infection, strongyloidiasis, subacute sclerosing panencephalitis, syphilis, taeniasis, tetanus, tinea barabe, tinea capitis, tinea corporis, tinea cruris, tinea manum, tinea nigra, tinea pedis, tinea unguium, tinea versicolor, toxocariasis, trachoma, toxoplasmosis, trichinosis, trichomoniasis, trichuriasis, tuberculosis, tularemia,
20 typhoid fever, *Ureaplasma urealyticum* infection, valley fever, Venezuelan hemorrhagic fever, viral pneumonia, West Nile fever, white piedra, *Yersinia pseudotuberculosis* infection, yersiniosis, yellow fever, and zygomycosis.

The chemical entity can be administered intratumorally.

The chemical entity can be administered systemically.

25 The methods can further include identifying the subject.

Other embodiments include those described in the Detailed Description and/or in the claims.

Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

As used herein, the term “NLRP3” is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous NLRP3 molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

As used herein, the term “TLR7” is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous TLR7 molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

As used herein, the term “TLR8” is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous TLR8 molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

“API” refers to an active pharmaceutical ingredient.

The term "IC50" or "EC50" refers an amount, concentration, or dosage of a compound that is required for 50% inhibition of a maximal response in an assay that measures such response.

5 The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a chemical entity (e.g., a compound exhibiting activity as a mitochondrial uncoupling agent or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as niclosamide or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound, such as a niclosamide analog, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof) being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study.

10 The term "excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See, e.g., *Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salts are not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described herein form with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

The term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components (referred to collectively herein as “excipients”), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the

art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

The term "subject" refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms
5 "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

The terms "treat," "treating," and "treatment," in the context of treating a disease or disorder, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to
10 slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof. The "treatment of cancer", refers to one or more of the following effects: (1) inhibition, to some extent, of tumor growth, including, (i) slowing down and (ii) complete growth arrest; (2) reduction in the number of tumor cells; (3) maintaining tumor size; (4) reduction in tumor size; (5) inhibition, including (i) reduction,
15 (ii) slowing down or (iii) complete prevention, of tumor cell infiltration into peripheral organs; (6) inhibition, including (i) reduction, (ii) slowing down or (iii) complete prevention, of metastasis; (7) enhancement of anti-tumor immune response, which may result in (i) maintaining tumor size, (ii) reducing tumor size, (iii) slowing the growth of a tumor, (iv) reducing, slowing or preventing invasion and/or (8) relief, to some extent, of
20 the severity or number of one or more symptoms associated with the disorder.

The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C₁₋₁₀
25 indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl.

The term "haloalkyl" refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halo.

The term "alkoxy" refers to an -O-alkyl radical (*e.g.*, -OCH₃).

The term "alkylene" refers to a branched or unbranched divalent alkyl (e.g., -CH₂-).

The term "heteroalkyl" refers to a branched or unbranched divalent alkyl containing the indicated number of heteroatoms (e.g., O or S), wherein each heteroatom is inserted
5 between two carbon atoms in the alkylene chain. A non-limiting example includes CH₂OCH₂CH₃.

The term "alkenyl" refers to a hydrocarbon chain that may be a straight chain or branched chain having one or more carbon-carbon double bonds. The alkenyl moiety contains the indicated number of carbon atoms. For example, C₂₋₆ indicates that the group
10 may have from 2 to 6 (inclusive) carbon atoms in it.

The term "alkynyl" refers to a hydrocarbon chain that may be a straight chain or branched chain having one or more carbon-carbon triple bonds. The alkynyl moiety contains the indicated number of carbon atoms. For example, C₂₋₆ indicates that the group
15 may have from 2 to 6 (inclusive) carbon atoms in it.

The term "aryl" refers to a 6-carbon monocyclic, 10-carbon bicyclic, or 14-carbon tricyclic aromatic ring system wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent, and wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic e.g. tetrahydronaphthyl. Examples of aryl groups also include phenyl, naphthyl and the
20 like.

The term "cycloalkyl" as used herein includes saturated cyclic hydrocarbon groups having 3 to 10 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group may be optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl,
25 cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S
30 if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each

ring may be substituted by a substituent, and wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic (but does not have to be a ring which contains a heteroatom, e.g. tetrahydroisoquinolinyl. Examples of heteroaryl groups also include pyridyl, furyl or
5 furanyl, imidazolyl, benzimidazolyl, pyrimidinyl, thiophenyl or thienyl, quinolinyl, indolyl, thiazolyl, and the like.

The term "heterocyclyl" refers to a nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms
10 selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like.

In addition, atoms making up the compounds of the present embodiments are
15 intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C .

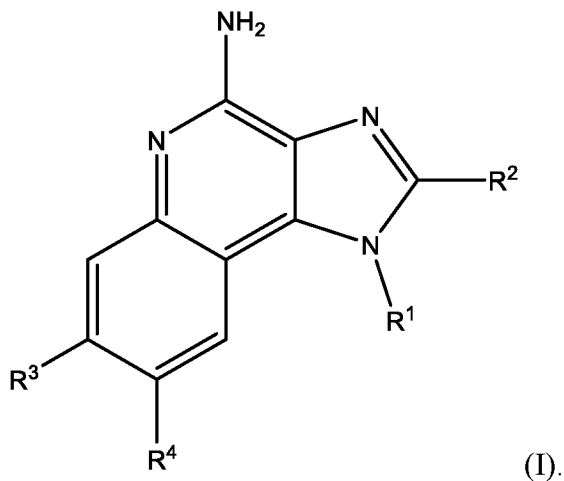
The details of one or more embodiments of the invention are set forth in the
20 accompanying drawings and the description below. Other features and advantages of the invention will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

This disclosure features chemical entities (e.g., a compound or a pharmaceutically
25 acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that modulate (e.g., agonize or partially agonize) NLRP3 and TLR7 and/or TLR8 that are useful, e.g., for treating a condition, disease or disorder in which a decrease in NLRP3 and TLR7 and/or TLR8 activities (e.g., a condition, disease or disorder associated with repressed or impaired NLRP3 and TLR7 and/or TLR8 signaling)

contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also features compositions as well as other methods of using and making the same.

5 In one aspect, compounds of Formula I, or a pharmaceutically acceptable salt thereof are featured:



In some embodiments, **R¹**, **R²**, **R³**, and **R⁴** are defined as follows:

10 **R¹** is hydrogen;

R² is:

(i) hydrogen;

(ii) unsubstituted, unbranched C₁₋₆ alkyl;

15 (iii) C₁₋₆ haloalkyl; or

(iv) heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

20

R^3 and R^4 are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo;
- (iii) cyano;
- 5 (iv) CO_2R^a ;
- (v) $CONR^bR^c$;
- (vi) C_{1-4} alkyl;
- (vii) C_{1-4} haloalkyl;
- (viii) C_{1-4} alkoxy; and
- 10 (ix) C_{1-4} haloalkoxy;

R^a is:

- (i) H;
- 15 (ii) C_{1-6} alkyl optionally substituted with from 1-2 substituents independently selected from $-OH$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl) $_2$, $-N(H)(C(=O)C_{1-3}$ alkyl), or cyano;
- (iii) C_{3-6} cycloalkyl optionally substituted with from 1-4 substituents independently selected from C_{1-6} alkyl, C_{1-4} haloalkyl, F, Cl, Br, $-OH$, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; or
- 20 (iv) benzyl, wherein the phenyl portion is optionally substituted with from 1-4 substituents independently selected from C_{1-6} alkyl, C_{1-4} haloalkyl, F, Cl, Br, $-OH$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, cyano, $CO_2(C_{1-6}$ alkyl); $-CONR^dR^e$, and $-NR^dR^e$;

each occurrence of R^b and R^c is independently selected from the group consisting of: H, C_{1-4} alkyl, $-C(O)(C_{1-4}$ alkyl), $-C(O)O(C_{1-4}$ alkyl), $-S(O)_{1-2}(R^f)$, $-C(O)NR^dR^e$, $-OH$, and C_{1-4} alkoxy; or R^b and R^c , together with the nitrogen atom to which each is attached forms heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of $N(R^g)$, O, and S, and wherein the heterocyclyl is optionally further substituted with from 1-4 R^h ,

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each occurrence of R^d and R^e is independently selected from the group consisting of: H and C₁₋₄ alkyl;

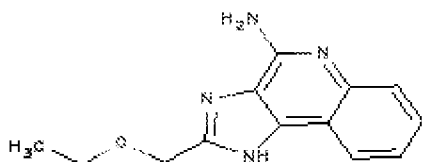
5 each occurrence of R^f is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, phenyl optionally substituted with from 1-3 R^m , and heteroaryl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heteroaryl is optionally substituted with from 1-3 R^m ;

10 each occurrence of R^g is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -C(O)NR^jR^k, -S(O)₁₋₂R^h, -OH, and C₁₋₄ alkoxy;

15 each occurrence of R^h is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, CO₂R^a; -CONR^jR^k, and -NR^jR^k; and

20 each occurrence of R^m is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, cyano, CO₂R^a; -CONR^dR^e, and -NR^dR^e.

In certain of these embodiments, it is provided that the compound is not:



25 In certain of these embodiments, it is provided that one of R^3 and R^4 is other than hydrogen.

In certain of these embodiments, it is provided R^1 is other than hydrogen.

In certain of these embodiments, it is provided that one of **R³** and **R⁴** is other than hydrogen, and **R¹** is other than hydrogen.

In other embodiments, **R¹**, **R²**, **R³**, and **R⁴** are defined as follows:

5

R¹ is:

(i) (C₁₋₃ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 **R^a**;

or

(ii) (C₁₋₃ alkylene)heteroaryl including from 5-6 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, and wherein the heteroaryl is optionally substituted with from 1-3 **R^a**;

10

R² is:

(i) hydrogen;

(ii) unsubstituted, unbranched C₁₋₆ alkyl;

15

(iii) C₁₋₆ haloalkyl; or

(iv) heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and

20

- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

R³ and **R⁴** are each independently selected from the group consisting of:

(i) hydrogen;

25

(ii) halo;

(iii) cyano;

(iv) CO₂R^b;

(v) CONR^cR^d;

(vi) C₁₋₄ alkyl;

30

(vii) C₁₋₄ haloalkyl;

(viii) C₁₋₄ alkoxy; and

(ix) C₁₋₄ haloalkoxy;

each occurrence of **R^a** is independently selected from the group consisting of:

5

(i) halo;

(ii) cyano;

(iii) C₁₋₆ alkyl optionally substituted with from 1-2 substituents independently selected from -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, -CO₂R^b; -CONR^cR^d, cyano, and -NR^cR^d;

10

(iv) C₂₋₆ alkenyl;

(v) C₂₋₆ alkynyl;

(vi) C₁₋₄ haloalkyl;

(vii) C₁₋₄ alkoxy;

(viii) C₁₋₄ haloalkoxy;

15

(ix) -(C₀₋₃ alkylene)-C₃₋₆ cycloalkyl optionally substituted with from 1-4 independently selected C₁₋₄ alkyl;

(x) -(C₀₋₃ alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected C₁₋₄ alkyl;

20

(xi) -(C₀₋₃ alkylene)-phenyl optionally substituted with from 1-3 R^e;

(xii) -(C₀₋₃ alkylene)-heteroaryl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heteroaryl is optionally substituted with from 1-3 R^e;

25

(xiii) -S(O)₁₋₂(R^h); and

(xiv) -NR^cR^d;

R^b is:

(i) H;

(ii) C₁₋₆ alkyl optionally substituted with from 1-2 substituents independently selected from -OH, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -N(H)(C(=O)C₁₋₃ alkyl), or cyano;

(iii) C₃₋₆ cycloalkyl optionally substituted with from 1-4 substituents independently selected from C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; or

(iv) benzyl, wherein the phenyl portion is optionally substituted with from 1-4 substituents independently selected from C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, cyano, -CO₂(C₁₋₆ alkyl); -CONR^fR^g, and -NR^fR^g;

each occurrence of **R^c** and **R^d** is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -S(O)₁₋₂(R^h), -C(O)NR^fR^g, -OH, and C₁₋₄ alkoxy; or **R^c** and **R^d**, together with the nitrogen atom to which each is attached forms heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R^j**), O, and S, and wherein the heterocyclyl is optionally further substituted with from 1-4 **R^k**,

each occurrence of **R^e** is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, cyano, CO₂R^b; -CONR^fR^g, and -NR^fR^g;

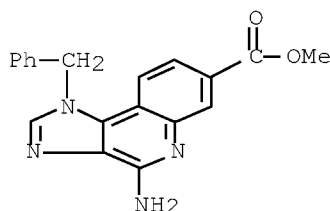
each occurrence of **R^f** and **R^g** is independently selected from the group consisting of: H and C₁₋₄ alkyl;

each occurrence of **R^h** is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, phenyl optionally substituted with from 1-3 **R^e**, and heteroaryl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heteroaryl is optionally substituted with from 1-3 **R^e**;

each occurrence of R^j is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -C(O)NR^fR^g, -S(O)₁₋₂R^h, -OH, and C₁₋₄ alkoxy; and

5 each occurrence of R^k is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, CO₂R^b; -CONR^fR^g, and -NR^fR^g

In certain of these embodiments, it is provided that the compound is not:



10

In certain of these embodiments, it is provided that one of R^3 and R^4 is other than hydrogen.

In certain of these embodiments, it is provided R^1 is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 R^a .

15 In certain of these embodiments, it is provided that one of R^3 and R^4 is other than hydrogen, and R^1 is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 R^a .

In still other embodiments, R^1 , R^2 , R^3 , and R^4 are defined as follows:

20 R^1 is X- R^5 , wherein X is unbranched C₂₋₆ alkylene or -O(unbranched C₂₋₆ alkylene)-, and R^5 is hydrogen, -OH, C₁₋₄ alkoxy, -C₁₋₄ alkoxy, CO₂R^a; -CONR^bR^c, cyano, or -NR^bR^c;

R^2 is:

- 25 (i) hydrogen;
 (ii) unsubstituted, unbranched C₁₋₆ alkyl;
 (iii) C₁₋₆ haloalkyl; or

(iv) heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

R³ and **R⁴** are each independently selected from the group consisting of:

(i) hydrogen;

(ii) halo;

(iii) cyano;

(iv) CO₂R^a;

(v) CONR^bR^c;

(vi) C₁₋₄ alkyl;

(vii) C₁₋₄ haloalkyl;

(viii) C₁₋₄ alkoxy; and

(ix) C₁₋₄ haloalkoxy;

R^a is:

(i) H;

(ii) C₁₋₆ alkyl optionally substituted with from 1-2 substituents independently selected from -OH, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -N(H)(C(=O)C₁₋₃ alkyl), or cyano;

(iii) C₃₋₆ cycloalkyl optionally substituted with from 1-4 substituents independently selected from C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; or

(iv) benzyl, wherein the phenyl portion is optionally substituted with from 1-4 substituents independently selected from C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, cyano, CO₂(C₁₋₆ alkyl); -CONR^dR^e, and -NR^dR^e;

each occurrence of R^b and R^c is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -S(O)₁₋₂(R^f), -C(O)NR^dR^e, -OH, and C₁₋₄ alkoxy; or R^b and R^c , together with the nitrogen atom to which each is attached forms heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each
 5 independently selected from the group consisting of N(R^g), O, and S, and wherein the heterocyclyl is optionally further substituted with from 1-4 R^h ,

each occurrence of R^d and R^e is independently selected from the group consisting of: H and C₁₋₄ alkyl;

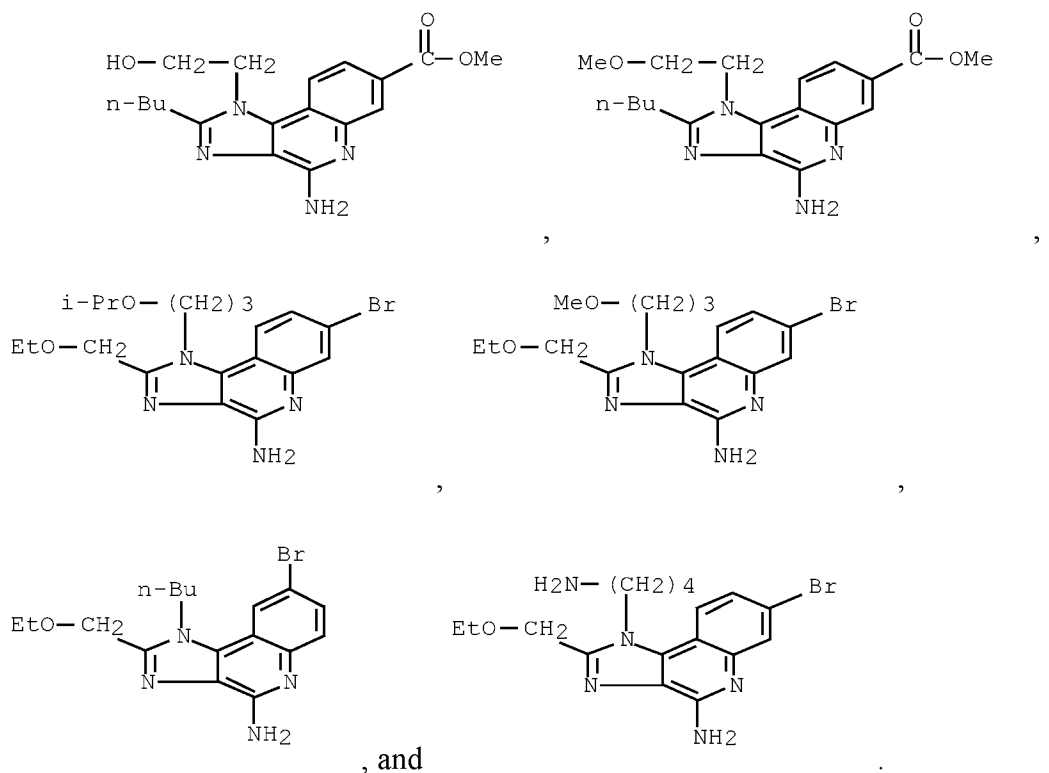
10 each occurrence of R^f is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, phenyl optionally substituted with from 1-3 R^m , and heteroaryl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heteroaryl is optionally substituted with from 1-3 R^m ;

15 each occurrence of R^g is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -C(O)NR^jR^k, -S(O)₁₋₂R^h, -OH, and C₁₋₄ alkoxy;

20 each occurrence of R^h is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, CO₂R^a, -CONR^jR^k, and -NR^jR^k; and

25 each occurrence of R^m is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, cyano, CO₂R^a, -CONR^dR^e, and -NR^dR^e.

In certain of these embodiments, it is provided that the compound is not:



- 5 In certain of these embodiments, one of R^3 and R^4 is other than hydrogen.
 In certain of these embodiments, X is -O(straight chain C_{2-6} alkylene)-.
 In certain of these embodiments, one of R^3 and R^4 is other than hydrogen, and X is -O(straight chain C_{2-6} alkylene)-.

10 **Variable R^2**

In some embodiments, R^2 is hydrogen.

In some embodiments, R^2 is unsubstituted, unbranched C_{1-6} alkyl (e.g., C_{2-5} , C_{2-4} , C_{3-5} , C_{3-4} , C_2 , C_3 , C_4). For example, R^2 can be *n*-butyl.

15

In some embodiments, R^2 is heteroalkyl, which includes from 3-8 (e.g., 3-6, 3-5, 3-4, 4) chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy.

5

In certain of these embodiments, **R²** is heteroalkyl, which includes from 3-8 (e.g., 3-6, 3-5, 3-4, 4) chain atoms, wherein 1 internal chain atom is O or S.

In certain of these embodiments, **R²** is heteroalkyl, which includes from 3-8 (e.g., 3-6, 3-5, 3-4, 4) chain atoms, wherein 1 internal chain atom is O.

10

In certain of these embodiments, **R²** is heteroalkyl, which includes from 3-5 chain atoms, wherein 1 internal chain atom is O. For example, **R²** can be $-\text{CH}_2\text{OCH}_2\text{CH}_3$.

Variables **R³** and **R⁴**

In some embodiments, **R³** and **R⁴** are each independently selected from the group consisting of:

15

- (i) hydrogen;
- (ii) halo;
- (iii) cyano;
- (iv) CO₂R^a; and
- (v) CONR^bR^c.

20

In certain embodiments, **R³** and **R⁴** are each independently selected from the group consisting of:

25

- (i) hydrogen;
- (ii) halo; and
- (iv) CO₂R^a.

In some embodiments, one of **R³** and **R⁴** is hydrogen, and the other is a substituent other than hydrogen.

In certain embodiments, one of **R³** and **R⁴** is hydrogen, and the other is halo or CO₂R^a.

30

In certain embodiments, one of R^3 and R^4 is hydrogen, and the other is halo (e.g., Br).

In certain embodiments, one of R^3 and R^4 is hydrogen, and the other is CO_2R^a .

In certain of these embodiments, R^a is C_{1-6} alkyl optionally substituted with $-OH$,
 5 $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, $-N(C_{1-3} \text{ alkyl})_2$, $-N(H)(C(=O)C_{1-3} \text{ alkyl})$, or cyano.

In certain of these embodiments, R^a is unsubstituted C_{1-6} alkyl (e.g., CH_3 or CH_2CH_3).

In some embodiments, R^3 is a substituent other than hydrogen, and R^4 is hydrogen.

10 In certain embodiments, R^3 is halo or CO_2R^a , and R^4 is hydrogen.

In certain embodiments, R^3 is halo (e.g., Br), and R^4 is hydrogen.

In certain embodiments, R^3 is CO_2R^a , and R^4 is hydrogen.

In certain of these embodiments, R^a is C_{1-6} alkyl optionally substituted with $-OH$,
 $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, $-N(C_{1-3} \text{ alkyl})_2$, $-N(H)(C(=O)C_{1-3} \text{ alkyl})$, or cyano.

15 In certain of these embodiments, R^a is unsubstituted C_{1-6} alkyl (e.g., CH_3 or CH_2CH_3).

In some embodiments, R^3 is hydrogen, and R^4 is hydrogen.

Variable R^1

20 In some embodiments, X is unbranched C_{2-4} alkylene. In some embodiments, X is unbranched C_{5-6} alkylene.

In some embodiments, X is unbranched $-O(C_{2-4} \text{ alkylene})-$. In some embodiments, X is unbranched $-O(C_{5-6} \text{ alkylene})-$.

25 In some embodiments, R^5 is $-OH$, C_{1-4} alkoxy, $-C_{1-4}$ haloalkoxy, CO_2R^a , or $-NR^bR^c$.

In certain embodiments, R^5 is $-OH$, C_{1-4} alkoxy, $-C_{1-4}$ haloalkoxy, or CO_2R^a .

In certain embodiments, R^5 is $-OH$.

In certain embodiments, R^5 is C_{1-4} alkoxy or $-C_{1-4}$ haloalkoxy (e.g., C_{1-4} alkoxy, e.g., OCH_3).

30 In certain embodiments, R^5 is CO_2R^a .

In certain of these embodiments, **R^a** is C₁₋₆ alkyl optionally substituted with -OH, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -N(H)(C(=O)C₁₋₃ alkyl), or cyano.

In certain of these embodiments, **R^a** is unsubstituted C₁₋₆ alkyl (e.g., CH₃ or CH₂CH₃).

5 In certain embodiments, **R⁵** is -NR^bR^c.

In certain of these embodiments, each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -S(O)₁₋₂(R^h), -C(O)NR^jR^k, -OH, and C₁₋₄ alkoxy.

10 In certain of these embodiments, each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -S(O)₁₋₂(R^h), and -C(O)NR^jR^k.

In certain of these embodiments, each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: H, C₁₋₄ alkyl, and -C(O)(C₁₋₄ alkyl).

15 In certain of these embodiments, each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: H and C₁₋₄ alkyl. For example, **R⁶** can be -NH₂, -N(H)(C₁₋₄ alkyl) (e.g., -NHCH₃) or -N(C₁₋₄ alkyl)₂ (e.g., -N(CH₃)₂).

In certain embodiments, **R¹** is (C₁₋₃ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 (e.g., 2, 1) **R^d**.

20 In certain embodiments, **R¹** is (C₁₋₃ alkylene)phenyl, wherein the phenyl is optionally substituted with from 1-3 (e.g., 2, 1) **R^d**.

In certain embodiments, **R¹** is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 (e.g., 2, 1) **R^d**.

25 In certain embodiments, **R¹** is (C₁₋₃ alkylene)phenyl, wherein the phenyl is substituted with from 1-3 (e.g., 2, 1) **R^d**.

In certain embodiments, **R¹** is (C₁₋₃ alkylene)phenyl, wherein the phenyl is substituted with 1 **R^d**.

30 In certain of these embodiments, **R^d**, or at least one **R^d** is C₁₋₆ (e.g., C₁₋₄, C₁₋₃, , C₁₋₂, C₁) alkyl optionally substituted with from 1-2 substituents independently selected from -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, -CO₂R^a, -CONR^bR^c, cyano, and -NR^bR^c.

In certain of these embodiments, R^d , or at least one R^d is C_{1-6} (e.g., C_{1-4} , C_{1-3} , C_{1-2} , C_1) alkyl substituted with from 1-2 substituents independently selected from -OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $-CO_2R^a$, $-CONR^bR^c$, cyano, and $-NR^bR^c$. By way of example, R^d can be $-CH_2NR^bR^c$, e.g., $-CH_2NH_2$.

5

Non-Limiting Combinations

[1] In some embodiments:

R^2 is unsubstituted, unbranched C_{1-6} alkyl; and

R^3 and R^4 are each independently selected from the group consisting of:

10

(i) hydrogen;

(ii) halo; and

(iv) CO_2R^a .

In certain of these embodiments, one of R^3 and R^4 is other than hydrogen.

15

[2] In some embodiments:

R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

20

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; and

R^3 and R^4 are each independently selected from the group consisting of:

25

(i) hydrogen;

(ii) halo; and

(iv) CO_2R^a .

In certain of these embodiments, one of R^3 and R^4 is other than hydrogen.

30

[3] In some embodiments:

R^1 is (C₁₋₃ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 R^a ;

R^2 is unsubstituted, unbranched C₁₋₆ alkyl; and

5 R^3 and R^4 are each independently selected from the group consisting of:

(i) hydrogen;

(ii) halo; and

(iv) CO₂R^a.

10 In certain of these embodiments, one of R^3 and R^4 is other than hydrogen.

In certain of these embodiments, R^1 is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 R^a .

In certain of these embodiments, one of R^3 and R^4 is other than hydrogen, and R^1 is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 R^a .

15

[4] In some embodiments:

R^1 is (C₁₋₃ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 R^a ;

20 R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
 - heteroalkyl is optionally substituted with from 1-4 substituents
- 25 independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; and

R^3 and R^4 are each independently selected from the group consisting of:

(i) hydrogen;

(ii) halo; and

30 (iv) CO₂R^a.

In certain of these embodiments, one of \mathbf{R}^3 and \mathbf{R}^4 is other than hydrogen.

In certain of these embodiments, \mathbf{R}^1 is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 \mathbf{R}^a .

5 In certain of these embodiments, one of \mathbf{R}^3 and \mathbf{R}^4 is other than hydrogen, and \mathbf{R}^1 is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 \mathbf{R}^a .

Embodiments of any one of combinations [1]-[4] can include one or more of the following features and apply to any of the \mathbf{R}^1 values delineated herein.

10 \mathbf{R}^2 can be *n*-butyl.

\mathbf{R}^2 can be heteroalkyl, which includes from 3-8 (e.g., 3-6, 3-5, 3-4, 4) chain atoms, wherein 1 internal chain atom is O or S.

\mathbf{R}^2 can be heteroalkyl, which includes from 3-8 (e.g., 3-6, 3-5, 3-4, 4) chain atoms, wherein 1 internal chain atom is O.

15 \mathbf{R}^2 can be heteroalkyl, which includes from 3-5 chain atoms, wherein 1 internal chain atom is O. For example, \mathbf{R}^2 can be $-\text{CH}_2\text{OCH}_2\text{CH}_3$.

\mathbf{X} can be unbranched C₂₋₄ alkylene or unbranched C₅₋₆ alkylene.

\mathbf{X} can be unbranched $-\text{O}(\text{C}_{2-4} \text{ alkylene})-$ or unbranched $-\text{O}(\text{C}_{5-6} \text{ alkylene})-$.

\mathbf{R}^5 can be $-\text{OH}$, $\text{CO}_2\mathbf{R}^a$; -or $-\text{NR}^b\mathbf{R}^c$.

20 \mathbf{R}^5 can be $-\text{NR}^b\mathbf{R}^c$.

Each occurrence of \mathbf{R}^b and \mathbf{R}^c can be independently selected from the group consisting of: H, C₁₋₄ alkyl, $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$, $-\text{S}(\text{O})_{1-2}(\mathbf{R}^h)$, $-\text{C}(\text{O})\text{NR}^j\mathbf{R}^k$, $-\text{OH}$, and C₁₋₄ alkoxy.

25 Each occurrence of \mathbf{R}^b and \mathbf{R}^c can be independently selected from the group consisting of: H, C₁₋₄ alkyl, $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$, $-\text{S}(\text{O})_{1-2}(\mathbf{R}^h)$, and $-\text{C}(\text{O})\text{NR}^j\mathbf{R}^k$.

Each occurrence of \mathbf{R}^b and \mathbf{R}^c can be independently selected from the group consisting of: H, C₁₋₄ alkyl, and $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$.

Each occurrence of R^b and R^c can be independently selected from the group consisting of: H and C_{1-4} alkyl. For example, R^6 can be $-NH_2$, $-N(H)(C_{1-4}$ alkyl) (e.g., $-NHCH_3$) or $-N(C_{1-4}$ alkyl)₂ (e.g., $-N(CH_3)_2$).

R^5 can be CO_2R^a . R^a can be C_{1-6} alkyl optionally substituted with $-OH$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)₂, $-N(H)(C(=O)C_{1-3}$ alkyl), or cyano; e.g., R^a can be unsubstituted C_{1-6} alkyl (e.g., CH_3 or CH_2CH_3).

R^5 can be $-OH$.

R^1 can be $(C_{1-3}$ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 (e.g., 2, 1) R^d .

R^1 can be $(C_{1-3}$ alkylene)phenyl, wherein the phenyl is optionally substituted with from 1-3 (e.g., 2, 1) R^d .

R^1 can be $(C_{1-3}$ alkylene)aryl, wherein the aryl is substituted with from 1-3 (e.g., 2, 1) R^d .

R^1 can be $(C_{1-3}$ alkylene)phenyl, wherein the phenyl is substituted with from 1-3 (e.g., 2, 1) R^d .

R^1 can be $(C_{1-3}$ alkylene)phenyl, wherein the phenyl is substituted with 1 R^d .

R^d , or at least one R^d can be C_{1-6} (e.g., C_{1-4} , C_{1-3} , C_{1-2} , C_1) alkyl optionally substituted with from 1-2 substituents independently selected from $-OH$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $-CO_2R^a$, $-CONR^bR^c$, cyano, and $-NR^bR^c$.

R^d , or at least one R^d can be C_{1-6} (e.g., C_{1-4} , C_{1-3} , C_{1-2} , C_1) alkyl substituted with from 1-2 substituents independently selected from $-OH$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $-CO_2R^a$, $-CONR^bR^c$, cyano, and $-NR^bR^c$. By way of example, R^d can be $-CH_2NR^bR^c$, e.g., $-CH_2NH_2$.

One of R^3 and R^4 (e.g., R^4) can be hydrogen, and the other (e.g., R^3) can be a substituent other than hydrogen.

One of R^3 and R^4 (e.g., R^4) can be hydrogen, and the other (e.g., R^3) can be halo or CO_2R^a .

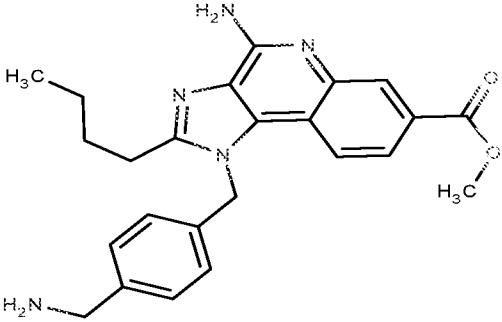
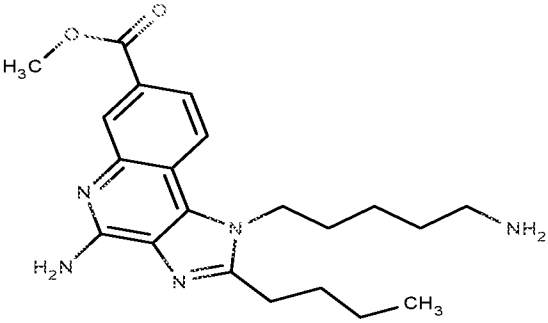
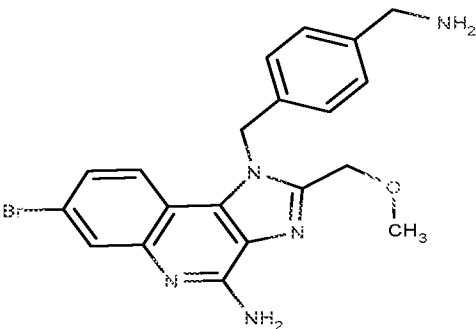
One of R^3 and R^4 (e.g., R^4) can be hydrogen, and the other (e.g., R^3) can be halo (e.g., Br).

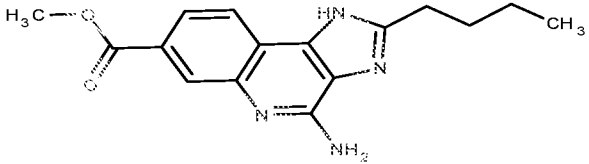
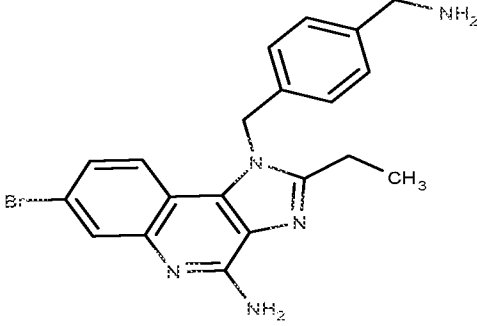
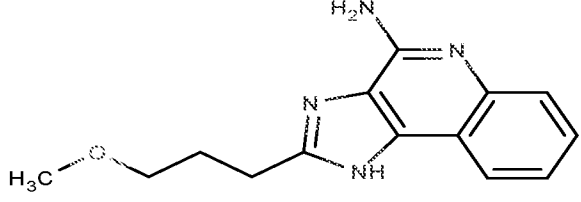
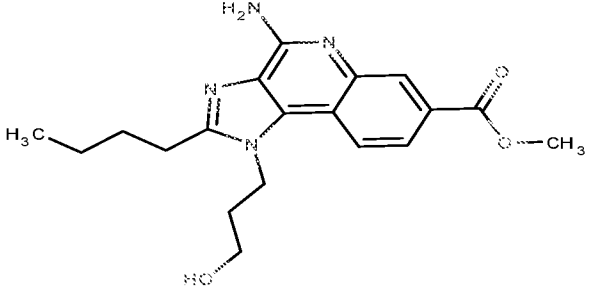
One of R^3 and R^4 (e.g., R^4) can be hydrogen, and the other (e.g., R^3) can be CO_2R^a . R^a can be C_{1-6} alkyl optionally substituted with $-OH$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl) $_2$, $-N(H)(C(=O)C_{1-3}$ alkyl), or cyano; e.g., R^a can be unsubstituted C_{1-6} alkyl (e.g., CH_3 or CH_2CH_3).

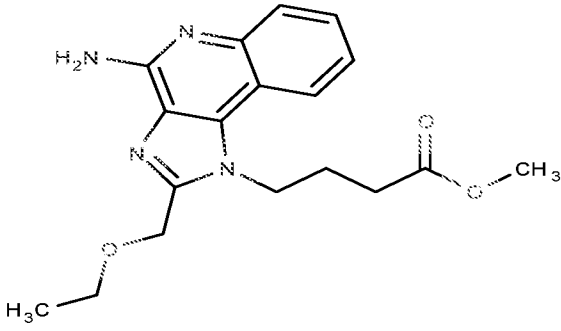
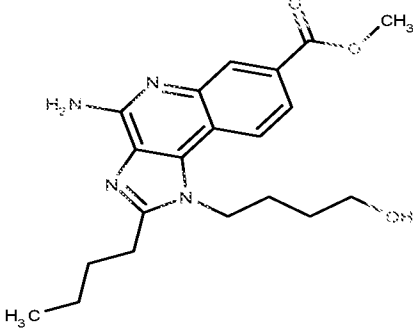
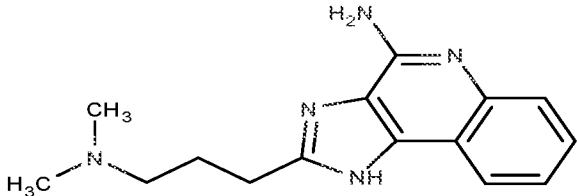
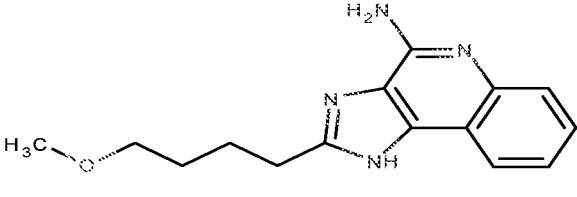
5 R^3 can be hydrogen, and R^3 can be hydrogen.

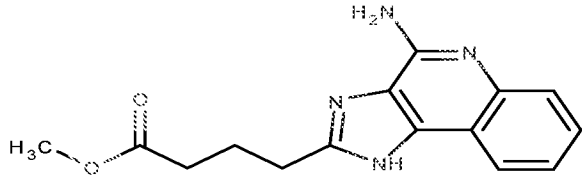
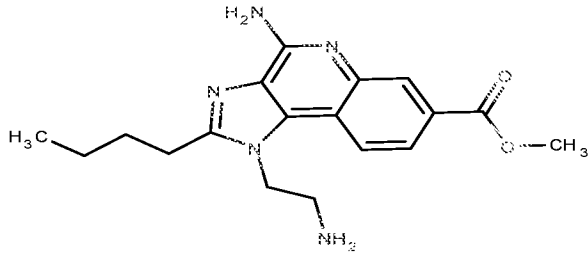
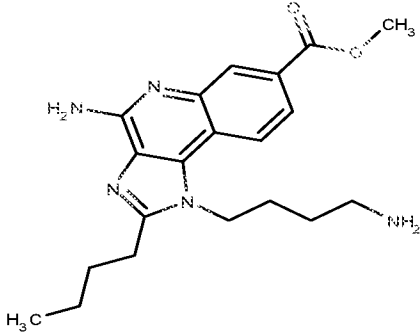
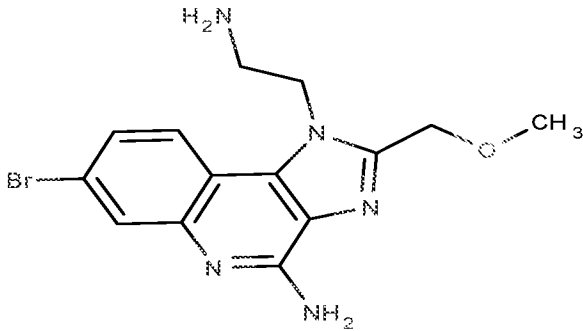
In some embodiments, the compound of Formula I is a compound selected from the group consisting of compounds in Table 1 below.

Table 1

Compound	Structure
101	
102	
103	

104	 <chem>COC(=O)c1ccc2c(c1)c(c[nH]2)NCCN</chem>
105	 <chem>CCNc1nc2c(c1)c(c[nH]2)BrC3=CC=C(C=C3)CN</chem>
106	 <chem>COCNc1nc2c(c1)c(c[nH]2)NCCN</chem>
107	 <chem>COC(=O)c1ccc2c(c1)c(c[nH]2)NCCN</chem>

108	
109	
110	
111	

<p>112</p>	
<p>113</p>	
<p>114</p>	
<p>115</p>	

Pharmaceutical Compositions and Administration

General

In some embodiments, a chemical entity (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination thereof) that modulates (e.g., agonizes or partially agonizes) NLRP3 and TLR7 and/or TLR8, is administered as a pharmaceutical composition that includes the chemical entity and one or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein.

In some embodiments, the chemical entities can be administered in combination with one or more conventional pharmaceutical excipients. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d- α -tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α -, β , and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a chemical entity as described herein in the range of 0.005% to 100% with the balance made up from non-toxic excipient may be prepared. The contemplated compositions may contain 0.001%-100% of a chemical entity provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 22nd Edition (Pharmaceutical Press, London, UK. 2012).

Routes of Administration and Composition Components

In some embodiments, the chemical entities described herein or a pharmaceutical composition thereof can be administered to subject in need thereof by any accepted route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, 5 intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, 10 intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal. In certain embodiments, a preferred route of administration is parenteral (e.g., 15 intratumoral).

Compositions can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes. Typically, such compositions can be prepared as injectables, either as liquid solutions or 20 suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the present disclosure.

The pharmaceutical forms suitable for injectable use include sterile aqueous 25 solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of 30 microorganisms, such as bacteria and fungi.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance
5 of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions
10 can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions
15 are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired
20 ingredient from a previously sterile-filtered solution thereof.

Intratumoral injections are discussed, e.g., in Lammers, et al., *“Effect of Intratumoral Injection on the Biodistribution and the Therapeutic Potential of HPMA Copolymer-Based Drug Delivery Systems” Neoplasia*. **2006**, *10*, 788–795.

Pharmacologically acceptable excipients usable in the rectal composition as a gel, cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of
30 polyethylene glycol Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate,

menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methoxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprate, isopropyl alcohol, propylene glycol, liquid
5 paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM) , lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

In certain embodiments, suppositories can be prepared by mixing the chemical entities described herein with suitable non-irritating excipients or carriers such as cocoa
10 butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum and release the active compound. In other embodiments, compositions for rectal administration are in the form of an enema.

15 In other embodiments, the compounds described herein or a pharmaceutical composition thereof are suitable for local delivery to the digestive or GI tract by way of oral administration (e.g., solid or liquid dosage forms.).

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the chemical entity is mixed with one or more
20 pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic
25 acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of
30 capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid

compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

5 In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a chemical entity provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, marume, solution or suspension (*e.g.*, in propylene carbonate, 10 vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more chemical entities provided herein or additional active agents are physically separated are also contemplated; *e.g.*, capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also 15 contemplated.

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid.

20 In certain embodiments the excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage form excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

25 In certain embodiments, solid oral dosage forms can further include one or more components that chemically and/or structurally predispose the composition for delivery of the chemical entity to the stomach or the lower GI; *e.g.*, the ascending colon and/or transverse colon and/or distal colon and/or small bowel. Exemplary formulation techniques are described in, *e.g.*, Filipski, K.J., et al., *Current Topics in Medicinal Chemistry*, **2013**, *13*, 776-802, which is incorporated herein by reference in its entirety.

Examples include upper-GI targeting techniques, e.g., Accordion Pill (Intec Pharma), floating capsules, and materials capable of adhering to mucosal walls.

Other examples include lower-GI targeting techniques. For targeting various regions in the intestinal tract, several enteric/pH-responsive coatings and excipients are available. These materials are typically polymers that are designed to dissolve or erode at specific pH ranges, selected based upon the GI region of desired drug release. These materials also function to protect acid labile drugs from gastric fluid or limit exposure in cases where the active ingredient may be irritating to the upper GI (e.g., hydroxypropyl methylcellulose phthalate series, Coateric (polyvinyl acetate phthalate), cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate, Eudragit series (methacrylic acid–methyl methacrylate copolymers), and Marcoat). Other techniques include dosage forms that respond to local flora in the GI tract, Pressure-controlled colon delivery capsule, and Pulsincap.

Ocular compositions can include, without limitation, one or more of any of the following: viscosogens (e.g., Carboxymethylcellulose, Glycerin, Polyvinylpyrrolidone, Polyethylene glycol); Stabilizers (e.g., Pluronic (triblock copolymers), Cyclodextrins); Preservatives (e.g., Benzalkonium chloride, ETDA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

Topical compositions can include ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the “internal” phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. As with

other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

In any of the foregoing embodiments, pharmaceutical compositions described herein can include one or more one or more of the following: lipids, interbilayer crosslinked multilamellar vesicles, biodegradable poly(D,L-lactic-co-glycolic acid) [PLGA]-based or poly anhydride-based nanoparticles or microparticles, and nanoporous particle-supported lipid bilayers.

Dosages

The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation can be determined by one skilled in the medical arts. The total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

In some embodiments, the compounds described herein are administered at a dosage of from about 0.001 mg/Kg to about 500 mg/Kg (e.g., from about 0.001 mg/Kg to about 200 mg/Kg; from about 0.01 mg/Kg to about 200 mg/Kg; from about 0.01 mg/Kg to about 150 mg/Kg; from about 0.01 mg/Kg to about 100 mg/Kg; from about 0.01 mg/Kg to about 50 mg/Kg; from about 0.01 mg/Kg to about 10 mg/Kg; from about 0.01 mg/Kg to about 5 mg/Kg; from about 0.01 mg/Kg to about 1 mg/Kg; from about 0.01 mg/Kg to about 0.5 mg/Kg; from about 0.01 mg/Kg to about 0.1 mg/Kg; from about 0.1 mg/Kg to about 200 mg/Kg; from about 0.1 mg/Kg to about 150 mg/Kg; from about 0.1 mg/Kg to about 100 mg/Kg; from about 0.1 mg/Kg to about 50 mg/Kg; from about 0.1 mg/Kg to about 10 mg/Kg; from about 0.1 mg/Kg to about 5 mg/Kg; from about 0.1 mg/Kg to about 1 mg/Kg; from about 0.1 mg/Kg to about 0.5 mg/Kg).

Regimens

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

5 In some embodiments, the period of administration of a compound described herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period
10 of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In an embodiment, a therapeutic compound is administered to an individual for a
15 period of time followed by a separate period of time. In another embodiment, a therapeutic compound is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where administration of the therapeutic compound is started and then a fourth period following the third period where administration is stopped. In an aspect of this embodiment, the
20 period of administration of a therapeutic compound followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In a further embodiment, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4
25 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8
30 months, 9 months, 10 months, 11 months, 12 months, or more.

Methods of Treatment

In some embodiments, methods for treating a subject having condition, disease or disorder in which a decrease or increase in NLRP3 activity (e.g., a decrease, e.g., repressed or impaired NLRP3 signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) are provided.

Indications

Cancer

In any of the methods described herein, the subject can have a cancer. In some examples of any of the methods described herein, the mammal has been identified as having a cancer, or has been diagnosed as having a cancer.

Non-limiting examples of cancer include: acute myeloid leukemia, adrenocortical carcinoma, Kaposi sarcoma, lymphoma, anal cancer, appendix cancer, teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain cancer, breast cancer, bronchial tumor, carcinoid tumor, cardiac tumor, cervical cancer, chordoma, chronic lymphocytic leukemia, chronic myeloproliferative neoplasm, colon cancer, colorectal cancer, craniopharyngioma, bile duct cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, eye cancer, fallopian tube cancer, gallbladder cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, germ cell tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hypopharyngeal cancer, pancreatic cancer, kidney cancer, laryngeal cancer, chronic myelogenous leukemia, lip and oral cavity cancer, lung cancer, melanoma, Merkel cell carcinoma, mesothelioma, mouth cancer, oral cancer, osteosarcoma, ovarian cancer, penile cancer, pharyngeal cancer, prostate cancer, rectal cancer, salivary gland cancer, skin cancer, small intestine cancer, soft tissue sarcoma, testicular cancer, throat cancer, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, and vulvar cancer.

Methods for diagnosing a subject as having a cancer or identifying a mammal as having a cancer are well known in the art. For example, a medical professional (e.g., a physician, a physician's assistant, or a technician) can diagnose cancer in a mammal by

observing one or more symptoms of cancer in a mammal. Non-limiting examples of symptoms of cancer include: fatigue, lump or area of thickening felt under the skin, weight change, jaundice, darkening or redness of the skin, sores that won't heal, changes to existing moles, changes in bowel or bladder habits, persistent cough or trouble breathing, difficulty swallowing, hoarseness, persistent indigestion or discomfort after eating, persistent, unexplained muscle or joint pain, persistent, unexplained fevers or night sweats, and unexplained bleeding or bruising. Methods of diagnosing a subject as having a cancer or identifying a subject as having a cancer can further include performing one or more diagnostic tests (e.g., performing one or more diagnostic tests on a biopsy or a blood sample).

In some examples of any of the methods described herein, a subject can be a subject having a cancer, a subject diagnosed as having a cancer, or a subject identified as having a cancer that has been unresponsive to a previously administered treatment for cancer. Diagnostic tests for diagnosing a subject as having a cancer or identifying a mammal as having a cancer are known in the art.

Infectious Disease

In any of the methods described herein, the subject can have an infectious disease. In some examples of any of the methods described herein, the subject has been identified as having an infectious disease, or has been diagnosed as having an infectious disease. For example, an infectious disease can be caused by a bacterium, virus, fungus, parasite, or a mycobacterium.

Non-limiting examples of infectious disease include: *Acinobacter* infection, actinomycosis, African sleeping sickness, acquired immunodeficiency syndrome, amebiasis, anaplasmosis, anthrax, *Arcanobacterium haemolyticum* infection, Argentine hemorrhagic fever, ascariasis, aspergillosis, astrovirus infection, babesiosis, *Bacillus cereus* infection, bacterial pneumonia, bacterial vaginosis, *Bacteroides* infection, balantidiasis, *Baylisascaris* infection, BK virus infection, black piedra, *Blastocystis hominis* infection, blastomycosis, Bolivian hemorrhagic fever, botulism, Brazilian hemorrhagic fever, brucellosis, bubonic plague, *Burkholderi* infection, Buruli ulcer,

Calicivirus infection, campylobacteriosis, candidiasis, cat-scratch disease, cellulitis, Chagas disease, chancroid, chickenpox, chikungunya, chlamydia, *Chlamydophila pneumoniae* infection, cholera, chromoblastomycosis, clonorchiasis, *Clostridium difficile* infection, coccidioidomycosis, Colorado tick fever, common cold, Creutzfeldt-Jakob disease, 5 Crimean-Congo hemorrhagic fever, cryptococcosis, cryptosporidiosis, cutaneous larva migrans, cyclosporiasis, cysticercosis, cytomegalovirus infection, dengue fever, *Desmodesmus* infection, deintamoebiasis, diphtheria, diphyllbothriasis, dracunculiasis, ebola hemorrhagic fever, echinococcosis, ehrlichiosis, enterobiasis, *Enterococcus* infection, *Enterovirus* infection, epidemic typhus, erythema infection, exanthema subitum, 10 fasciolopsiasis, fasciolosis, fatal familial insomnia, filariasis, food poisoning by *Clostridium myonecrosis*, free-living amebic infection, *Fusobacterium* infection, gas gangrene, geotrichosis, Gerstmann-Sträussler-Scheinker syndrome, giardiasis, glanders, gnathostomiasis, gonorrhea, granuloma inguinale, Group A streptococcal infection, Group B streptococcal infection, *Haemophilus influenzae* infection, hand foot and mouth disease, 15 hantavirus pulmonary syndrome, Heartland virus disease, *Helicobacter pylori* infection, hemolytic-uremic syndrome, hemorrhagic fever with renal syndrome, hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, herpes simplex, histoplasmosis, hookworm infection, human bocavirus infection, human ewingii ehrlichiosis, human granulocyte anaplasmosis, human metapneumovirus infection, human monocytic ehrlichiosis, human 20 papillomavirus infection, human parainfluenza virus infection, hymenolepiasis, Epstein-Barr virus infectious mononucleosis, influenza, isosporiasis, Kawasaki disease, keratitis, *Kingella kingae* infection, kuru, lassa fever, Legionnaires' disease, Pontiac fever, leishmaniasis, leprosy, leptospirosis, listeriosis, lyme disease, lymphatic filariasis, lymphocytic choriomeningitis, malaria, Marburg hemorrhagic fever, measles, Middle East 25 respiratory syndrome, melioidosis, meningitis, meningococcal disease, metagonimiasis, microsporidiosis, molluscum contagiosum, monkeypox, mumps, murine typhus, mycoplasma pneumonia, mycetoma, myiasis, neonatal conjunctivitis, variant Creutzfeldt-Jakob disease, nocardiosis, onchocerciasis, paracoccidioidomycosis, paragonimiasis, pasteurellosis, pediculosis capitis, pediculosis corporis, pediculosis pubis, pelvic 30 inflammatory disease, pertussis, plague, pneumonia, poliomyelitis, *Prevotella* infection,

primary amoebic meningoencephalitis, progressive multifocal leukoencephalopathy, psittacosis, Q fever, rabies, relapsing fever, respiratory syncytial virus infection, rhinosporidiosis, rhinovirus infection, rickettsial infection, rickettsialpox, Rift Valley Fever, Rocky Mountain spotted fever, rotavirus infection, rubella, salmonellosis, severe acute respiratory syndrome, scabies, schistosomiasis, sepsis, shigellosis, shingles, smallpox, sporothrichosis, staphylococcal food poisoning, staphylococcal infection, staphylococcal infection, strongyloidiasis, subacute sclerosing panencephalitis, syphilis, taeniasis, tetanus, tinea barabe, tinea capitis, tinea corporis, tinea cruris, tinea manum, tinea nigra, tinea pedis, tinea unguium, tinea versicolor, toxocariasis, trachoma, toxoplasmosis, trichinosis, trichomoniasis, trichuriasis, tuberculosis, tularemia, typhoid fever, *Ureaplasma urealyticum* infection, valley fever, Venezuelan hemorrhagic fever, viral pneumonia, West Nile fever, white piedra, *Yersinia pseudotuberculosis* infection, yersiniosis, yellow fever, and zygomycosis.

Exemplary infections by foreign agents which may be treated and/or prevented by the method of the present invention include an infection by a bacterium (e.g., a Gram-positive or Gram-negative bacterium), an infection by a fungus, an infection by a parasite, and an infection by a virus. In one embodiment of the present invention, the infection is a bacterial infection (e.g., infection by *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella spp.*, *Staphylococcus aureus*, *Streptococcus spp.*, or vancomycin-resistant enterococcus). In another embodiment, the infection is a fungal infection (e.g. infection by a mould, a yeast, or a higher fungus). In still another embodiment, the infection is a parasitic infection (e.g., infection by a single-celled or multicellular parasite, including *Giardia duodenalis*, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, and *Toxoplasma gondii*). In yet another embodiment, the infection is a viral infection (e.g., infection by a virus associated with AIDS, avian flu, chickenpox, cold sores, common cold, flavivirus infections gastroenteritis, glandular fever, influenza, measles, mumps, pharyngitis, pneumonia, rubella, SARS, and lower or upper respiratory tract infection (e.g., respiratory syncytial virus)).

Methods for diagnosing a subject as having an infectious disease, or identifying a subject as having an infectious disease are well known in the art. For example, a medical

professional (e.g., a physician, a physician's assistant, or a technician) can diagnose infectious disease in a subject by observing one or more symptoms of infectious disease in a subject. Non-limiting examples of symptoms of infectious disease include: fever, diarrhea, fatigue, and muscle aches. Methods of diagnosing a mammal as having an infectious disease or identifying a subject as having an infectious disease can further include performing one or more diagnostic tests (e.g., performing one or more diagnostic tests on a biopsy or a blood sample). Diagnostic tests for diagnosing a subject as having an infectious disease or identifying a subject as having an infectious disease are known in the art.

Vaccine Adjuvant

In some embodiments, the chemical entities described herein activate one or more adaptive immune responses, e.g., by inducing production of T helper 1 -polarizing cytokines. As such, this disclosure contemplates the use of the chemical entities described herein adjuvants for vaccines, e.g., for the very young and/or the elderly.

In one aspect, methods of improving vaccination are featured. In some embodiments, the methods include administering to a subject, according to any one or more of the regimens described herein, a chemical entity described herein (e.g., and a vaccine agent (e.g., as a single vaccine or in separate compositions according to a vaccination protocol). As used herein, the "vaccine agent" is an entity (e.g., having an antigen) to which the vaccine provides for immunogenicity thereto. The chemical entity can be administered in an amount sufficient to function as an adjuvant with regard to the vaccine agent.

In certain embodiments, said methods increase production of inflammatory cytokines in the subject.

In certain embodiments, said methods up-regulate major histocompatibility complex (MHC) molecules and/or co-stimulatory signals in antigen-presenting cells in the subject.

In certain embodiments, said methods activate natural killer (NK) cells in the subject.

In certain embodiments, said methods cause an adaptive immune response in the subject to the vaccine agent.

In certain embodiments, said methods induce production of T helper 1 -polarizing cytokines in the subject.

5 In certain embodiments, said methods evoke a dominant pro-inflammatory cytokine profile including tumor necrosis factor- α (TNF- α), interleukin-12 (IL-12), and IL-18 and/or upregulate the production of Th1 -polarizing cytokines TNF- α and IL-12 in neonatal antigen presenting cells.

10 In certain embodiments, the subject is a youth under 10, 5, 4, 3, 2, or 1 years of age or a newborn younger than 12 months, 6 months, 4 months, 3 months, 2 months, or 1 month. In other embodiments, the subject is elderly above 50 years of age (e.g., above 55 years of age, above 60 years of age over 62 years of age, over 65 years of age, over 67 years of age, over 70 years of age, over 75 years of age, over 80 years of age, over 85 years of age, over 90 years of age).

15 In another aspect, methods of activating an immune system are featured, which include administering immunological agent to a subject along with a chemical entity described herein in amount sufficient to function as an adjuvant with regard to the immunological agent.

In certain embodiments, the vaccine can be a cancer vaccine.

20

Other Indications

In one aspect, methods of treating allergic bronchitis are featured, which include administering to a subject (e.g., in need thereof) a chemical entity described herein.

25 In one aspect, methods of treating bronchospastic disorder are featured, which include administering to a subject (e.g., in need thereof) a chemical entity described herein.

In one aspect, methods of treating hepatitis, such as hepatitis C (e.g., HCV), are featured, which include administering to a subject (e.g., in need thereof) a chemical entity described herein.

30 In one aspect, methods of treating bronchial asthma are featured, which include administering to a subject (e.g., in need thereof) a chemical entity described herein.

In one aspect, methods of treating atopic bronchitis are featured, which include administering to a subject (e.g., in need thereof) a chemical entity described herein.

In one aspect, methods of activating a cytotoxic T lymph response are featured, which include administering to a subject (e.g., in need thereof) a chemical entity described
5 herein.

In some embodiments, the condition, disease or disorder is an autoimmune diseases. Non-limiting examples include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel diseases (IBDs) comprising Crohn disease (CD) and ulcerative colitis (UC), which are chronic inflammatory conditions with
10 polygenic susceptibility. In certain embodiments, the condition is an inflammatory bowel disease. In certain embodiments, the condition is Crohn's disease, autoimmune colitis, iatrogenic autoimmune colitis, ulcerative colitis, colitis induced by one or more chemotherapeutic agents, colitis induced by treatment with adoptive cell therapy, colitis associated by one or more alloimmune diseases (such as graft-vs-host disease, e.g., acute
15 graft vs. host disease and chronic graft vs. host disease), radiation enteritis, collagenous colitis, lymphocytic colitis, microscopic colitis, and radiation enteritis. In certain of these embodiments, the condition is alloimmune disease (such as graft-vs-host disease, e.g., acute graft vs. host disease and chronic graft vs. host disease), celiac disease, irritable bowel syndrome, rheumatoid arthritis, lupus, scleroderma, psoriasis, cutaneous T-cell
20 lymphoma, uveitis, and mucositis (e.g., oral mucositis, esophageal mucositis or intestinal mucositis).

In some embodiments, the condition, disease or disorder is mucositis, also known as stomatitis, which can occur as a result of chemotherapy or radiation therapy, either alone or in combination as well as damage caused by exposure to radiation outside of the
25 context of radiation therapy.

In some embodiments, the condition, disease or disorder is uveitis, which is inflammation of the uvea (e.g., anterior uveitis, e.g., iridocyclitis or iritis; intermediate uveitis (also known as pars planitis); posterior uveitis; or chorioretinitis, e.g., pan-uveitis).

Combination Therapy

This disclosure contemplates both monotherapy regimens as well as combination therapy regimens.

5 In some embodiments, the methods described herein can further include administering one or more additional therapies (e.g., one or more additional therapeutic agents and/or one or more therapeutic regimens) in combination with administration of the compounds described herein.

10 In certain embodiments, the methods described herein can further include administering one or more additional cancer therapies.

The one or more additional cancer therapies can include, without limitation, surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy, cancer vaccines (e.g., HPV vaccine, hepatitis B vaccine, Oncophage, Provenge) and gene therapy, as well as combinations thereof. Immunotherapy, including, without limitation, adoptive
15 cell therapy, the derivation of stem cells and/or dendritic cells, blood transfusions, lavages, and/or other treatments, including, without limitation, freezing a tumor.

In some embodiments, the one or more additional cancer therapies is chemotherapy, which can include administering one or more additional chemotherapeutic agents.

20

In certain embodiments, the additional chemotherapeutic agent is an immunomodulatory moiety, e.g., an immune checkpoint inhibitor. In certain of these embodiments, the immune checkpoint inhibitor targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70-CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM – LIGHT, HVEM–

25

BTLA-CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS-ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2-TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA-CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or PD-L1) and other immunomodulatory agents, such as interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming growth factor- β (TGF β), CD39, CD73 Adenosine-CD39-CD73, and CXCR4-CXCL12. See, e.g., Postow, M. *J. Clin. Oncol.* **2015**, *33*, 1.

In certain of these embodiments, the immune checkpoint inhibitor is selected from the group consisting of: Urelumab, PF-05082566, MEDI6469, TRX518, Varlilumab, CP-870893, Pembrolizumab (PD1), Nivolumab (PD1), Atezolizumab (formerly MPDL3280A) (PDL1), MEDI4736 (PD-L1), Avelumab (PD-L1), PDR001 (PD1), BMS-986016, MGA271, Lirilumab, IPH2201, Emactuzumab, INCB024360, Galunisertib, Ulocuplumab, BKT140, Bavituximab, CC-90002, Bevacizumab, and MNRP1685A, and MGA271.

In certain embodiments, the additional chemotherapeutic agent is a STING agonist. For example, the STING agonist can include cyclic di-nucleotides, such as cAMP, cGMP, and cGAMP as well as modified cyclic di-nucleotides that include one or more of the following modification features (2'-O/3'-O linkage, phosphorothioate linkage, adenine and/or guanine analogue, 2'-OH modification or replacement). See, e.g., WO 2014/189805.

In certain embodiments, the additional chemotherapeutic agent is an alkylating agent. Alkylating agents are so named because of their ability to alkylate many nucleophilic functional groups under conditions present in cells, including, but not limited to cancer cells. In a further embodiment, an alkylating agent includes, but is not limited to, Cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin. In an embodiment, alkylating agents can function by impairing cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules or they can work by modifying a cell's DNA. In a further embodiment an alkylating agent is a synthetic, semisynthetic or derivative.

In certain embodiments, the additional chemotherapeutic agent is an anti-metabolite. Anti-metabolites masquerade as purines or pyrimidines, the building-blocks of DNA and in general, prevent these substances from becoming incorporated in to DNA during the "S" phase (of the cell cycle), stopping normal development and division. Anti-metabolites can also affect RNA synthesis. In an embodiment, an antimetabolite includes, but is not limited to azathioprine and/or mercaptopurine. In a further embodiment an anti-metabolite is a synthetic, semisynthetic or derivative.

In certain embodiments, the additional chemotherapeutic agent is a plant alkaloid and/or terpenoid. These alkaloids are derived from plants and block cell division by, in general, preventing microtubule function. In an embodiment, a plant alkaloid and/or terpenoid is a vinca alkaloid, a podophyllotoxin and/or a taxane. Vinca alkaloids, in general, bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules, generally during the M phase of the cell cycle. In an embodiment, a vinca alkaloid is derived, without limitation, from the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*). In an embodiment, a vinca alkaloid includes, without limitation, Vincristine, Vinblastine, Vinorelbine and/or Vindesine. In an embodiment, a taxane includes, but is not limited, to Taxol, Paclitaxel and/or Docetaxel. In a further embodiment a plant alkaloid or terpenoid is a synthetic, semisynthetic or derivative. In a further embodiment, a podophyllotoxin is, without limitation, an etoposide

and/or teniposide. In an embodiment, a taxane is, without limitation, docetaxel and/or ortataxel. In an embodiment, a cancer therapeutic is a topoisomerase. Topoisomerases are essential enzymes that maintain the topology of DNA. Inhibition of type I or type II topoisomerases interferes with both transcription and replication of DNA by upsetting
5 proper DNA supercoiling. In a further embodiment, a topoisomerase is, without limitation, a type I topoisomerase inhibitor or a type II topoisomerase inhibitor. In an embodiment a type I topoisomerase inhibitor is, without limitation, a camptothecin. In another embodiment, a camptothecin is, without limitation, exatecan, irinotecan, lurtotecan, topotecan, BNP 1350, CKD 602, DB 67 (AR67) and/or ST 1481. In an embodiment, a type
10 II topoisomerase inhibitor is, without limitation, epipodophyllotoxin. In a further embodiment an epipodophyllotoxin is, without limitation, an ansacrine, etoposid, etoposide phosphate and/or teniposide. In a further embodiment a topoisomerase is a synthetic, semisynthetic or derivative, including those found in nature such as, without limitation, epipodophyllotoxins, substances naturally occurring in the root of American
15 Mayapple (*Podophyllum peltatum*).

In certain embodiments, the additional chemotherapeutic agent is a stilbenoid. In a further embodiment, a stilbenoid includes, but is not limited to, Resveratrol, Piceatannol, Pinosylin, Pterostilbene, Alpha-Viniferin, Ampelopsin A, Ampelopsin E, Diptoindonesin
20 C, Diptoindonesin F, Epsilon- Viniferin, Flexuosol A, Gnetin H, Hemsleyanol D, Hopeaphenol, Trans-Diptoindonesin B, Astringin, Piceid and Diptoindonesin A. In a further embodiment a stilbenoid is a synthetic, semisynthetic or derivative.

In certain embodiments, the additional chemotherapeutic agent is a cytotoxic
25 antibiotic. In an embodiment, a cytotoxic antibiotic is, without limitation, an actinomycin, an anthracenedione, an anthracycline, thalidomide, dichloroacetic acid, nicotinic acid, 2-deoxyglucose and/or chlofazimine. In an embodiment, an actinomycin is, without limitation, actinomycin D, bacitracin, colistin (polymyxin E) and/or polymyxin B. In another embodiment, an anthracenedione is, without limitation, mitoxantrone and/or
30 pixantrone. In a further embodiment, an anthracycline is, without limitation, bleomycin,

doxorubicin (Adriamycin), daunorubicin (daunomycin), epirubicin, idarubicin, mitomycin, plicamycin and/or valrubicin. In a further embodiment a cytotoxic antibiotic is a synthetic, semisynthetic or derivative.

5 In certain embodiments, the additional chemotherapeutic agent is selected from endostatin, angiogenin, angiostatin, chemokines, angioarrestin, angiostatin (plasminogen fragment), basement-membrane collagen-derived anti-angiogenic factors (tumstatin, canstatin, or arrestin), anti-angiogenic antithrombin III, signal transduction inhibitors, cartilage-derived inhibitor (CDI), CD59 complement fragment, fibronectin fragment, gro-
10 beta, heparinases, heparin hexasaccharide fragment, human chorionic gonadotropin (hCG), interferon alpha/beta/gamma, interferon inducible protein (IP-10), interleukin-12, kringle 5 (plasminogen fragment), metalloproteinase inhibitors (TIMPs), 2-methoxyestradiol, placental ribonuclease inhibitor, plasminogen activator inhibitor, platelet factor-4 (PF4), prolactin 16 kD fragment, proliferin-related protein (PRP), various retinoids,
15 tetrahydrocortisol-S, thrombospondin-1 (TSP-1), transforming growth factor-beta (TGF- β), vasculostatin, vasostatin (calreticulin fragment) and the like.

 In certain embodiments, the additional chemotherapeutic agent is selected from abiraterone acetate, altretamine, anhydrovinblastine, auristatin, bexarotene, bicalutamide,
20 BMS 184476, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulfonamide, bleomycin, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, cachectin, cemadotin, chlorambucil, cyclophosphamide, 3',4'-didehydro-4'-deoxy-8'-norvin-caleukoblastine, docetaxol, doxetaxel, cyclophosphamide, carboplatin, carmustine, cisplatin, cryptophycin, cyclophosphamide, cytarabine, dacarbazine (DTIC),
25 dactinomycin, daunorubicin, decitabine dolastatin, doxorubicin (adriamycin), etoposide, 5-fluorouracil, finasteride, flutamide, hydroxyurea and hydroxyureataxanes, ifosfamide, liarozole, lonidamine, lomustine (CCNU), MDV3100, mechlorethamine (nitrogen mustard), melphalan, mivobulin isethionate, rhizoxin, sertenef, streptozocin, mitomycin, methotrexate, taxanes, nilutamide, onapristone, paclitaxel, prednimustine, procarbazine,

RPR109881, stramustine phosphate, tamoxifen, tasonermin, taxol, tretinoin, vinblastine, vincristine, vindesine sulfate, and vinflunine.

In certain embodiments, the additional chemotherapeutic agent is platinum, cisplatin, carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil, azathioprine, mercaptopurine, vincristine, vinblastine, vinorelbine, vindesine, etoposide and teniposide, paclitaxel, docetaxel, irinotecan, topotecan, amsacrine, etoposide, etoposide phosphate, teniposide, 5-fluorouracil, leucovorin, methotrexate, gemcitabine, taxane, leucovorin, mitomycin C, tegafur-uracil, idarubicin, fludarabine, mitoxantrone, ifosfamide and doxorubicin. Additional agents include inhibitors of mTOR (mammalian target of rapamycin), including but not limited to rapamycin, everolimus, temsirolimus and deforolimus.

In still other embodiments, the additional chemotherapeutic agent can be selected from those delineated in U.S. Patent 7,927,613, which is incorporated herein by reference in its entirety.

In yet another embodiment, the methods can further include administering one or both of: (i) one or more anti-fungal agents (e.g., selected from the group of bifonazole, butoconazole, clotrimazole, econazole, ketoconazole, luliconazole, miconazole, omoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, albaconazole, efinaconazole, epoziconazole, fluconazole, isavuconazole, itraconazole, posaconazole, propiconazole, ravusconazole, terconazole, voriconazole, abafungin, amorolfin, butenafine, naftifine, terbinafine, anidulafungin, caspofungin, micafungin, benzoic acid, ciclopirox, flucytosine, 5-fluorocytosine, griseofulvin, haloprogin, tolnaflate, undecylenic acid, and balsam of peru) and (ii) one or more antibiotics (e.g., selected from the group of amikacin, gentamicin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, spectinomycin, geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem, cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalothin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten,

ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, dalbavancin, oritavancin, clindamycin, lincomycin, daptomycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazolidone, nitrofurantoin, linezolid, posizolid, radezolid, torezolid, amoxicillin, ampicillin, azlocillin, carbenicillin, clocxacillin, diclocxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, penicillin G, temocillin, ticarcillin, amoxicillin, calvulanate, ampicillin, subbactam, piperacillin, tazobactam, ticarcillin, clavulanate, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole, sulfonamideochrysoidine, demeclocycline, minocycline, oytetracycline, tetracycline, clofazimine, dapsone, dapreomycin, cycloserine, ethambutol, ethionamide, isoniazid, pyrazinamide, rifampicin, rifabutin, rifapentine, streptomycin, arsphenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin, dalopristin, thiamphenicol, tigecycline, tinidazole, trimethoprim, and teixobactin).

In yet another embodiment, the methods can further include administering one or anti-viral agents, e.g., selected from the group consisting of an interferon, a nucleotide analogue, a polymerase inhibitor, an NS3 protease inhibitor, an NS5A inhibitor, an entry inhibitor, a non-nucleoside polymerase inhibitor, a cyclosporine immune inhibitor, an NS4A antagonist, an NS4B-RNA binding inhibitor, a locked nucleic acid mRNA inhibitor, a cyclophilin inhibitor, and combinations thereof.

In certain embodiments, the second therapeutic agent or regimen is administered to the subject prior to contacting with or administering the chemical entity (e.g., about one hour prior, or about 6 hours prior, or about 12 hours prior, or about 24 hours prior, or about 48 hours prior, or about 1 week prior, or about 1 month prior).

In other embodiments, the second therapeutic agent or regimen is administered to the subject at about the same time as contacting with or administering the chemical entity. By way of example, the second therapeutic agent or regimen and the chemical entity are provided to the subject simultaneously in the same dosage form. As another example, the
5 second therapeutic agent or regimen and the chemical entity are provided to the subject concurrently in separate dosage forms.

In still other embodiments, the second therapeutic agent or regimen is administered to the subject after contacting with or administering the chemical entity (e.g., about one hour after, or about 6 hours after, or about 12 hours after, or about 24 hours after, or about
10 48 hours after, or about 1 week after, or about 1 month after).

Patient Selection

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of such treatment (e.g., by way of biopsy, endoscopy, or other conventional method known in the art). In certain embodiments, the
15 NLRP3 protein can serve as a biomarker for certain types of cancer.

In some embodiments, the chemical entities, methods, and compositions described herein can be administered to certain treatment-resistant patient populations (e.g., patients
20 resistant to checkpoint inhibitors).

Compound Preparation and Biological Assays

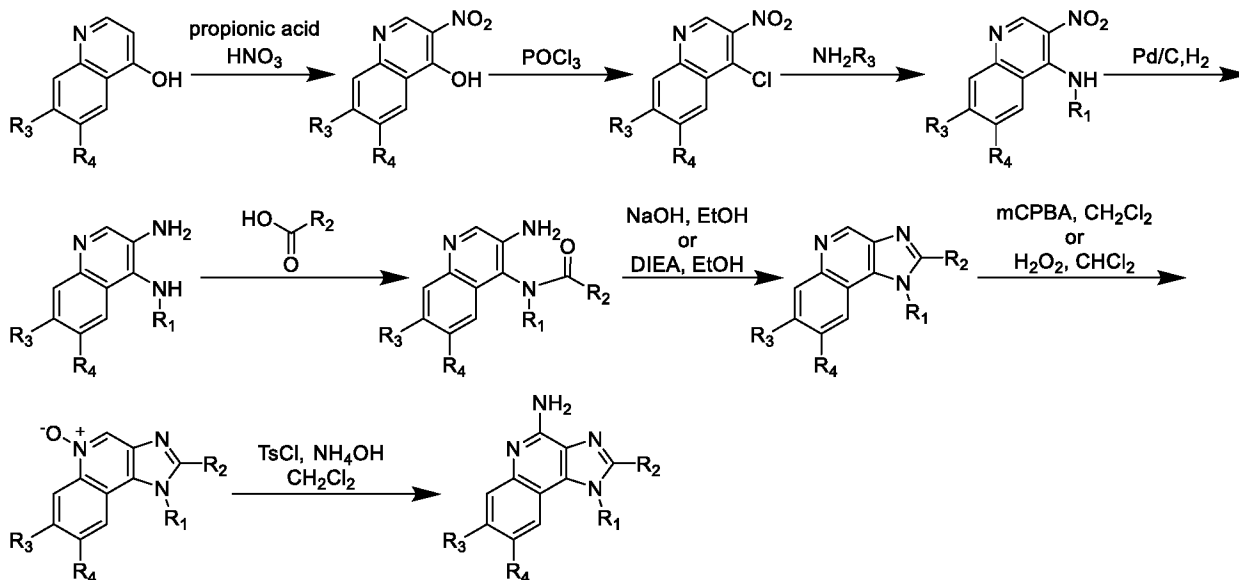
As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and
25 deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and RGM. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser,
30 Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L.

Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

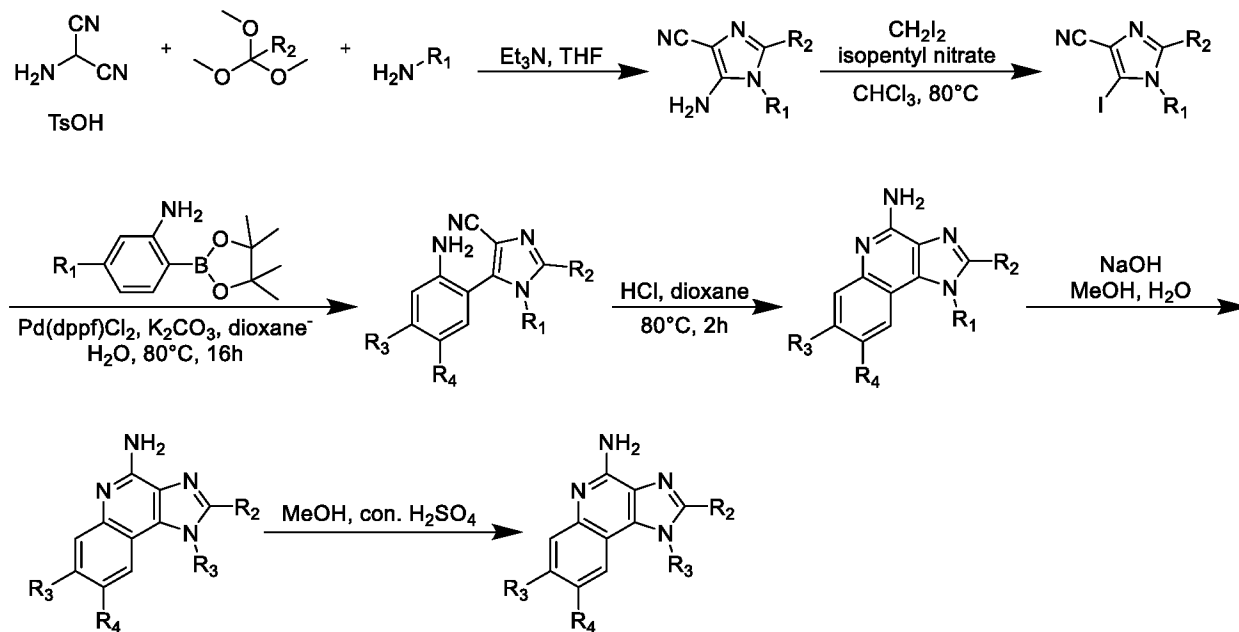
Schemes 1 and 2 show examples of methods of preparation of compounds disclosed herein:

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Scheme 1

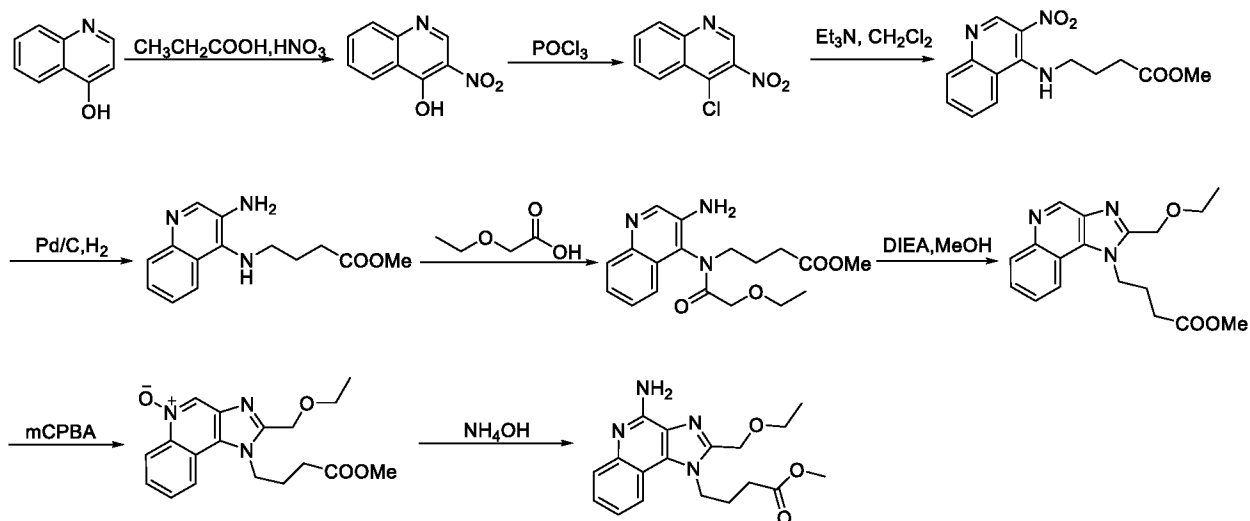


Scheme 2



Representative Preparative Examples

Preparative example 1 – Compound 108



5

1. Synthesis of 3-nitroquinolin-4-ol

Into a 100-mL round-bottom flask was placed a solution of quinolin-4-ol (4 g, 27.56 mmol, 1.00 equiv) in $\text{CH}_3\text{CH}_2\text{COOH}$ (30 mL). This was followed by the addition of HNO_3 (1.77 mL). The resulting solution was stirred overnight at 125°C in an oil bath. The reaction mixture was cooled to room temperature and poured into water/ice. The precipitated solid was collected by filtration, washed with water and ethanol, and dried. This resulted in 3.414 g (65%) of 3-nitroquinolin-4-ol as a yellow solid.

LC-MS: (ES, m/z): $[\text{M}+\text{H}]^+ = 191.0$

15

2. Synthesis of 4-chloro-3-nitroquinoline

Into a 100-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-nitroquinolin-4-ol (1.9 g, 10.00 mmol, 1.00 equiv), N,N -dimethylformamide (876 mg, 12.00 mmol, 1.20 equiv) and POCl_3 (3.648 g, 23.79 mmol, 2.00 equiv) in dichloromethane (20 mL). The resulting solution was stirred for 4 h at 45°C in an oil bath. The reaction was then quenched by the addition

20

of ice/water. The resulting solution was extracted with dichloromethane (3x50 mL) and washed with aqueous NaHCO₃ (1x50 mL), dried over Na₂SO₄ and concentrated under vacuum. This resulted in 2.295 g of crude 4-chloro-3-nitroquinoline as a yellow solid.

LC-MS: (ES, *m/z*): [M+H]⁺ = 209.0

5 **3. Synthesis of methyl 4-[(3-nitroquinolin-4-yl)amino]butanoate**

Into a 50-mL round-bottom flask was placed a solution of methyl 4-aminobutanoate hydrochloride (673.2 g, 4.4 mol, 1.10 equiv) and trimethylamine (TEA, 2.2 g, 20.0 mmol, 5.00 equiv) in dichloromethane (15 mL). This was followed by addition of 4-chloro-3-nitroquinoline (832 mg, 4.0 mmol, 1.00 equiv). The resulting
10 solution was stirred overnight at 45°C in an oil bath. The reaction was then quenched by the addition of brine. The resulting solution was extracted with dichloromethane (3x30 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 936 mg (crude) of methyl 4-[(3-nitroquinolin-4-
15 yl)amino]butanoate as a yellow oil.

LC-MS: (ES, *m/z*): [M+H]⁺ = 290.1

4. Synthesis of methyl 4-[(3-aminoquinolin-4-yl)amino]butanoate

Into a 100-mL round-bottom flask was placed a solution of methyl 4-[(3-nitroquinolin-4-yl)amino]butanoate (936 mg, 3.24 mmol, 1.00 equiv) in
20 tetrahydrofuran/MeOH (25/25 mL). To the solution was added palladium on carbon (187 mg). The solution was degassed and back filled with hydrogen. The solution was stirred overnight at room temperature. The resulting solution was diluted with 30 mL of methanol, filtered, and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 610 mg (73%) of
25 methyl 4-[(3-aminoquinolin-4-yl)amino]butanoate as a yellow oil.

LC-MS: (ES, *m/z*): [M+H]⁺ = 260.1

5. Synthesis of methyl 4-[N-(3-aminoquinolin-4-yl)-2-ethoxyacetamido]butanoate

Into a 50-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-ethoxyacetic acid (245 mg, 2.35 mmol, 1.00 equiv), N,N-diisopropylethylamine (DIEA, 456 mg, 3.53 mmol, 1.50 equiv) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 1.34 g, 3.52 mmol, 1.50 equiv) in dichloromethane (15 mL). The resulting solution was stirred for 1.5 h at 0°C in a water/ice bath. A solution of methyl 4-[(3-aminoquinolin-4-yl)amino]butanoate (610 mg, 2.35 mmol, 1.00 equiv) in dichloromethane (5 mL) was added dropwise to the solution. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of brine. The resulting solution was extracted with dichloromethane (3x30 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 352 mg (43%) of methyl 4-[N-(3-aminoquinolin-4-yl)-2-ethoxyacetamido]butanoate as a yellow oil.

LC-MS: (ES, *m/z*): [M+H]⁺ = 346.2

6. Synthesis of Methyl 4-[2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]butanoate

Into a 25-mL round-bottom flask, was placed a solution of methyl 4-[N-(3-aminoquinolin-4-yl)-2-ethoxyacetamido]butanoate (345 mg, 1.00 mmol, 1.00 equiv) and DIEA (4 mL) in methanol (8 mL). The resulting solution was stirred for 3 h at 70°C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 137 mg (42%) of methyl 4-[2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]butanoate as yellow oil.

LC-MS-PH-IFM-N-1-018-0: (ES, *m/z*): [M+H]⁺ = 328.2

H-NMR-PH-IFM-N-1-018-0: (CDCl₃, 300 MHz, ppm): δ 9.29 (s, 1H), 8.37-8.28 (m, 2H), 7.71-7.68 (m, 2H), 4.87 (s, 2H), 4.73 (t, *J* = 7.8 Hz, 2H), 3.74 (s, 3H), 3.63 (q, *J* = 6.9 Hz, 2H), 2.58-2.54 (m, 2H), 2.34-2.29 (m, 2H), 1.24 (t, *J* = 6.9 Hz, 3H).

7. Synthesis of 2-(ethoxymethyl)-1-(4-methoxy-4-oxobutyl)-1H-imidazo[4,5-c]quinolin-5-ium-5-olate

Into a 50-mL round-bottom flask, was placed a solution of methyl 4-[2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]butanoate (137 mg, 0.42 mmol, 1.00 equiv) in chloroform (15 mL). To the solution was added mCPBA (96 mg, 0.56 mmol, 1.50 equiv). The resulting solution was stirred overnight at 65°C in an oil bath. The resulting solution was diluted with 25 mL of dichloromethane, washed with brine (3x15 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). This resulted in 111 mg (77%) of 2-(ethoxymethyl)-1-(4-methoxy-4-oxobutyl)-1H-imidazo[4,5-c]quinolin-5-ium-5-olate as yellow oil.

LC-MS-PH-IFM-N-1-013-5: (ES, *m/z*): [M+H]⁺ = 344.2

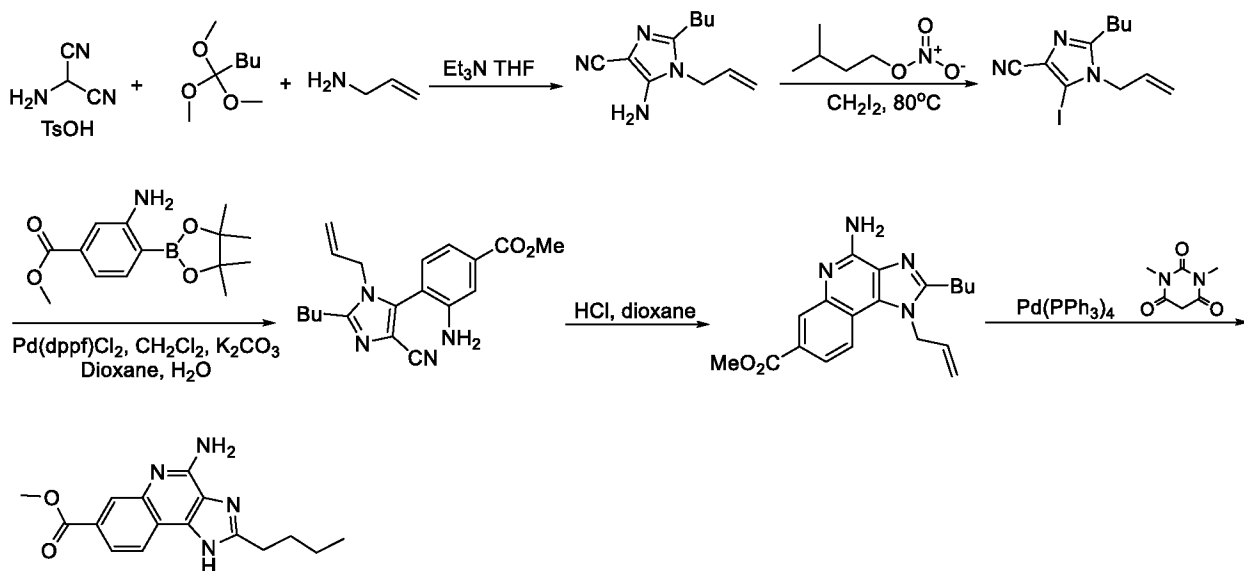
8. Synthesis of Methyl 4-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]butanoate

Into a 25-mL round-bottom flask, was placed a solution of 2-(ethoxymethyl)-1-(4-methoxy-4-oxobutyl)-1H-imidazo[4,5-c]quinolin-5-ium-5-olate (111 mg, 0.32 mmol, 1.00 equiv) and NH₄OH (2.5 mL) in dichloromethane (5 mL). This is followed by addition of TsCl (92 mg, 0.48 mmol, 1.50 equiv) at 0°C. The resulting solution was stirred overnight at room temperature. After removing the solvent, the crude product was purified by Prep-HPLC with the following conditions (Prep_HPLC_17): Column, X Bridge C18 OBD Prep Column, 10 μm, 19 mm X 250 mm; mobile phase, Water (10MMOL/L NH₄HCO₃) and ACN (30.0% ACN up to 43.0% in 7 min); Detector, UV 254/220nm. This resulted in 55.5 mg (50%) of methyl 4-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]butanoate as a white solid.

LC-MS-PH-IFM-N-1-013-0: (ES, *m/z*): [M+H]⁺ = 343.2

H-NMR-PH-IFM-N-1-013-0: (CDCl₃, 400 MHz, ppm): δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.57-7.53 (m, 1H), 7.40-7.36 (m, 1H), 5.60 (brs, 2H), 4.81 (s, 2H), 4.66 (t, *J* = 8.0 Hz, 2H), 3.74 (s, 3H), 3.63 (q, *J* = 6.8 Hz, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.34-2.27 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H).

5 Preparative example 2 – Compound 104



1. Synthesis of 1-allyl-5-amino-2-butyl-1H-imidazole-4-carbonitrile

Into a 50-mL round-bottom flask was placed a solution of 2-aminopropanedinitrile-4-methylbenzene-1-sulfonic acid (2 g, 7.90 mmol, 1.00 equiv) in tetrahydrofuran (30 mL). To the solution was added TEA (960 mg, 9.49 mmol, 1.20 equiv). The reaction mixture was stirred at room temperature for 30 min. 1,1,1-trimethoxy-2-methylbutane (1.56 g, 9.62 mmol, 1.20 equiv) was then added to the reaction and the reaction was stirred at 80°C for an additional 3 h. The reaction mixture was then cooled to room temperature, followed by addition of TEA (960 mg, 9.49 mmol, 1.20 equiv) and prop-2-en-1-amine (546 mg, 9.58 mmol, 1.20 equiv) to the mixture. The resulting solution was allowed to react, with stirring, for an additional 4 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (10:1). This resulted in 1.2 g (74%) of 1-allyl-5-amino-2-butyl-1H-imidazole-4-carbonitrile as a brown oil.

LC-MS: (ES, m/z): $[M+H]^+ = 205.1$

2. Synthesis of 1-allyl-2-butyl-5-iodo-1H-imidazole-4-carbonitrile

Into a 50-mL round-bottom flask was placed a solution of 1-allyl-5-amino-2-butyl-1H-imidazole-4-carbonitrile (1.2 g, 5.88 mmol, 1.00 equiv) in CH_2I_2 (10 mL). The mixture was heated to 80°C. Then isopentyl nitrate (2.8 g, 23.90 mmol, 4.00 equiv) was added to the mixture slowly. The resulting solution was stirred for 4 h at 80°C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (9:1). This resulted in 420 mg (23%) of 1-allyl-2-butyl-5-iodo-1H-imidazole-4-carbonitrile as a brown oil.

LC-MS: (ES, m/z): $[M+H]^+ = 316.0$

3. Synthesis of methyl 4-(1-allyl-2-butyl-4-cyano-1H-imidazol-5-yl)-3-aminobenzoate

Into a 50-mL round-bottom flask was placed a solution of 1-allyl-2-butyl-5-iodo-1H-imidazole-4-carbonitrile (420 mg, 1.30 mmol, 1.00 equiv) and methyl 3-amino-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate hydrochloride (610 mg, 1.95 mmol, 1.50 equiv) in dioxane (10 mL) and water (0.1 mL). To the solution were added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 95 mg, 0.10 equiv) and potassium carbonate (538 mg, 3.89 mmol, 3.00 equiv) under nitrogen. The resulting solution was stirred for 2 h at 80°C. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (9:1). This resulted in 210 mg (48%) of methyl 4-(1-allyl-2-butyl-4-cyano-1H-imidazol-5-yl)-3-aminobenzoate as a brown solid.

LC-MS: (ES, m/z): $[M+H]^+ = 339.2$

4. Synthesis of methyl 1-allyl-4-amino-2-butyl-1H-imidazo[4,5-c]quinoline-7-carboxylate

Into a 50-mL round-bottom flask was placed a mixture of methyl 4-(1-allyl-2-butyl-4-cyano-1H-imidazol-5-yl)-3-aminobenzoate (210 mg, 0.62 mmol, 1.00 equiv) and 4N HCl in dioxane (5 mL). The resulting solution was stirred for 5 h at 80°C. After

removing the solvent, the residue was applied onto a silica gel column with ethyl acetate/petroleum ether (9:1). This resulted in 180 mg (86%) of methyl 1-allyl-4-amino-2-butyl-1H-imidazo[4,5-c]quinoline-7-carboxylate as a brown oil.

LC-MS: (ES, m/z): $[M+H]^+ = 339.2$

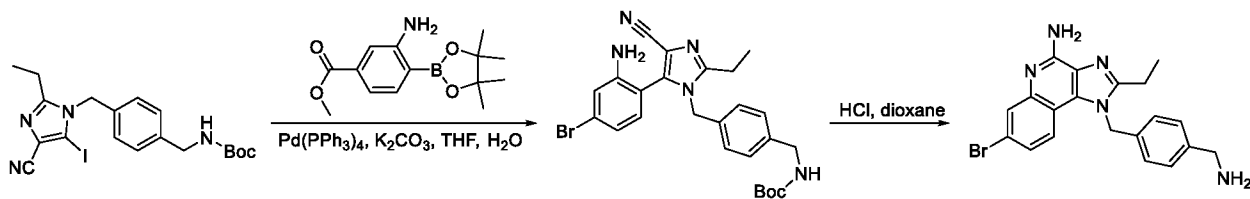
5 **5. Synthesis of Methyl 4-amino-2-butyl-1H-imidazo[4,5-c]quinoline-7-carboxylate**

Into a 50-mL round-bottom flask was placed a solution of methyl 1-allyl-4-amino-2-butyl-1H-imidazo[4,5-c]quinoline-7-carboxylate (180 mg, 0.53 mmol, 1.00 equiv) in tetrahydrofuran (THF, 20 mL). To the solution were added Pd(PPh₃)₄ (61 mg, 0.053 mmol, 0.10 equiv) and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (165 mg, 1.06 mmol, 2.00 equiv). The resulting solution was stirred for 5 h at 80°C. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (HPLC-10): column, X Bridge C18 OBD Prep Column, 100Å, 10 μm, 19 mm x 250 mm; mobile phase, water (10 mmol/L NH₄HCO₃) and acetonitrile (ACN, 30% ACN up to 47% in 10 min); detector, UV 254/220 nm. This resulted in 69.2 mg (44%) of methyl 4-amino-2-butyl-1H-imidazo[4,5-c]quinoline-7-carboxylate as an off-white solid.

LC-MS: (ES, m/z): $[M+H]^+ = 299.3$

¹H-NMR: (DMSO-*d*₆, 400 MHz) δ 8.16 (s, 1H), 8.12-8.05 (m, 1H), 7.77 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 2.92 (t, J = 7.2 Hz, 2H), 1.84-1.78 (m, 2H), 1.38 (p, J = 7.1 Hz, 2H), 0.96-0.92 (m, 3H).

Preparative example 3 – Compound 105



25 **1. Synthesis of tert-butyl N-[(4-[[5-(2-amino-4-bromophenyl)-4-cyano-2-ethyl-1H-imidazol-1-yl]methyl]phenyl)methyl]carbamate**

To a solution of tert-butyl N-([4-[(4-cyano-2-ethyl-5-iodo-1H-imidazol-1-yl)methyl] phenyl] methyl) carbamate (200 mg, 0.429 mmol, 1.00 equiv) in tetrahydrofuran and water (8 mL/2 mL) were added (2-amino-4-bromophenyl)boronic acid (120 g, 0.558 mmol, 1.30 equiv), potassium carbonate (138 mg, 1.29 mmol, 3.00 equiv) and Pd(PPh₃)₄ (70 mg, 0.086 mmol, 0.20 equiv) under N₂. The resulting solution was stirred for 6 h at 80°C under N₂. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was purified by chromatography on silica-gel eluting with ethyl acetate/petroleum ether (2:1). This resulted in 80 mg of tert-butyl N-([4-[[5-(2-amino-4-bromophenyl)-4-cyano-2-ethyl-1H-imidazol-1-yl]methyl]phenyl)methyl]carbamate as a white solid.

LC-MS: (ES, *m/z*): [M+1]⁺ = 510.1.

2. Synthesis of 1-[[4-(aminomethyl)phenyl]methyl]-7-bromo-2-ethyl-1H-imidazo[4,5-c]quinolin-4-amine

Into a 50-mL round-bottom flask was placed a solution of tert-butyl N-([4-[[5-(2-amino-4-bromophenyl)-4-cyano-2-ethyl-1H-imidazol-1-yl]methyl] phenyl] methyl)carbamate (80 mg, 0.16 mmol, 1.00 equiv) in hydrogen chloride/dioxane (10 mL, 4 mol/L). The solution was stirred for 3 h at 80°C. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (HPLC-10): column, X Bridge C18 OBD Prep Column, 10 μm, 19 mm x 250 mm; mobile phase, water (10 mmol/L NH₄HCO₃) and ACN (20.0% ACN up to 60.0% in 8 min); detector, UV 254 nm. This resulted in 28 mg (44%) of 1-[[4-(aminomethyl)phenyl]methyl]-7-bromo-2-ethyl-1H-imidazo[4,5-c]quinolin-4-amine as a white solid.

LC-MS: (ES, *m/z*): [M+1]⁺ = 409.9

¹H NMR: (300 MHz, DMSO-*d*₆): δ 7.73-7.67 (m, 2H), 7.25-7.14 (m, 3H), 6.90 (d, J = 8.1 Hz, 2H), 5.77 (s, 2H), 3.59 (s, 2H), 2.88 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.5 Hz, 3H).

Bioassays:**Inhibition of IL-1 β production in PMA-differentiated THP-1 cells**

THP-1 cells were purchased from the American Type Culture Collection and sub-cultured according to instructions from the supplier. Prior to experiments, cells were
5 cultured in RPMI 1640 containing 10% heat inactivated FBS, penicillin (100 units/mL) and streptomycin (100 μ g/mL), and maintained in log phase prior to experimental setup. Prior to the experiment, THP-1 were treated with PMA (phorbol 12-myristate 13-acetate) (10 μ g/mL) for 24 hours. The day of the experiment, the media was removed and attaching cells were treated with trypsin for 2 minutes. Cells were then collected, washed
10 with PBS (phosphate buffer saline), spun down, resuspended in 2% heat inactivated FBS with RPMI at a concentration of 1×10^6 cells/mL, and 100 μ L was plated in a 96-well plate. Cells were incubated with compounds for 4 hours. Cell-free supernatant was collected and the production of IL-1 β was evaluated by ELISA. Compounds were dissolved in dimethyl sulfoxide (DMSO) and added to the culture medium to achieve the
15 desired concentration (e.g., 100, 30, 10, 3, 1, 0.3 or 0.1 μ M). A vehicle-only control was run concurrently with each experiment. Final DMSO concentration was 1%. Compounds exhibited a dose-related increase of IL-1 β production in PMA-differentiated THP-1 cells

EC₅₀ values (μ M) of compounds of the formulae herein tested in accordance with the protocol above gave EC₅₀ values of less than about 60 μ M.

**Inhibition of Secreted Alkaline Phosphatase production to assess activity on
20 TLR7 and TLR8**

HEK-Blue TLR7 and HEK-Blue TLR8 were purchased from Invivogen and sub-cultured according to instructions from the supplier. HEK-Blue cells were incubated at a density of $\sim 2.2 \times 10^5$ cells per mL in a volume of 90 μ L per well, in 96-well flat-bottomed
25 plates in HEK-Blue detection media (Invivogen) and subsequently stimulated with graded concentrations of compounds for 24 hours. SAP (serum amyloid P component) was assayed spectrophotometrically using an alkaline phosphatase-specific chromogen at 620 nm. Compounds were dissolved in dimethyl sulfoxide (DMSO) and added to the culture medium to achieve desired concentration (e.g., 100, 30, 10, 3, 1, 0.3 or 0.1 μ M). A vehicle-

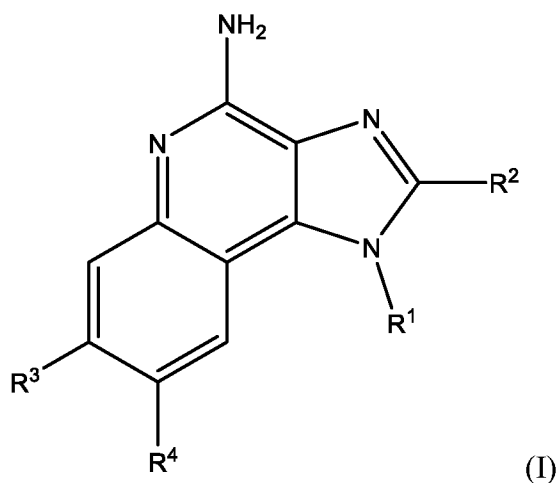
only control was run concurrently with each experiment. Final DMSO concentration was 1%. Compounds exhibited a dose-related activation of TLR7, or of TLR8, or of both TLR7 and TLR8, or did not induce TLR7 or TLR8 activation.

5 EC₅₀ values (μM) of compounds of the formulae herein tested in accordance with the protocol above gave EC₅₀ values of less than about 30 μM.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of
10 the following claims.

WHAT IS CLAIMED IS:

1. A compound having formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

R¹ is hydrogen;

R² is:

(i) hydrogen;

(ii) unsubstituted, unbranched C₁₋₆ alkyl;

(iii) C₁₋₆ haloalkyl; or

(iv) heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

R³ and **R⁴** are each independently selected from the group consisting of:

(i) hydrogen;

- (ii) halo;
- (iii) cyano;
- (iv) CO₂R^a;
- (v) CONR^bR^c;
- (vi) C₁₋₄ alkyl;
- (vii) C₁₋₄ haloalkyl;
- (viii) C₁₋₄ alkoxy; and
- (ix) C₁₋₄ haloalkoxy;

R^a is:

- (i) H;
- (ii) C₁₋₆ alkyl optionally substituted with from 1-2 substituents independently selected from -OH, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -N(H)(C(=O)C₁₋₃ alkyl), or cyano;
- (iii) C₃₋₆ cycloalkyl optionally substituted with from 1-4 substituents independently selected from C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; or
- (iv) benzyl, wherein the phenyl portion is optionally substituted with from 1-4 substituents independently selected from C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, cyano, CO₂(C₁₋₆ alkyl); -CONR^dR^e, and -NR^dR^e;

each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -S(O)₁₋₂(R^f), -C(O)NR^dR^e, -OH, and C₁₋₄ alkoxy; or **R^b** and **R^c**, together with the nitrogen atom to which each is attached forms heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R^g**), O, and S, and wherein the heterocyclyl is optionally further substituted with from 1-4 **R^h**,

each occurrence of R^d and R^e is independently selected from the group consisting of: H and C_{1-4} alkyl;

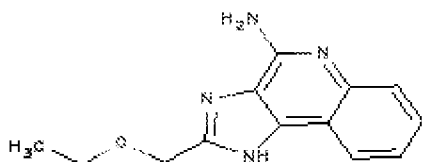
each occurrence of R^f is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, phenyl optionally substituted with from 1-3 R^m , and heteroaryl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heteroaryl is optionally substituted with from 1-3 R^m ;

each occurrence of R^g is independently selected from the group consisting of: H, C_{1-4} alkyl, $-C(O)(C_{1-4}$ alkyl), $-C(O)O(C_{1-4}$ alkyl), $-C(O)NR^jR^k$, $-S(O)_{1-2}R^h$, $-OH$, and C_{1-4} alkoxy;

each occurrence of R^h is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-4} haloalkyl, F, $-OH$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, CO_2R^a ; $-CONR^jR^k$, and $-NR^jR^k$; and

each occurrence of R^m is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-4} haloalkyl, F, Cl, Br, $-OH$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, cyano, CO_2R^a ; $-CONR^dR^e$, and $-NR^dR^e$; and

provided the compound is not:



2. The compound of claim 1, wherein one of R^3 and R^4 is other than hydrogen.

3. The compound of claim 1 or 2, wherein R^2 is hydrogen.
4. The compound of claim 1 or 2, wherein R^2 is unsubstituted, unbranched C_{1-6} alkyl.
5. The compound of claim 4, wherein R^2 is *n*-butyl.
6. The compound of claim 1 or 2, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:
 - when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
 - heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.
7. The compound of claim 6, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O or S.
8. The compound of claim 7, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O.
9. The compound of claim 8, wherein R^2 is heteroalkyl, which includes from 3-5 chain atoms, wherein 1 internal chain atom is O.
10. The compound of claim 8, wherein R^2 is $-CH_2OCH_2CH_3$.
11. The compound of any one of claims 1-10, wherein R^3 and R^4 are each independently selected from the group consisting of:
 - (i) hydrogen;
 - (ii) halo;

- (iii) cyano;
- (iv) CO₂R^a; and
- (v) CONR^bR^c.

12. The compound of any one of claims 1-11, wherein **R³** and **R⁴** are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo; and
- (iv) CO₂R^a.

13. The compound of any one of claims 1-12, wherein one of **R³** and **R⁴** is hydrogen, and the other is a substituent other than hydrogen.

14. The compound of any one of claims 1-13, wherein one of **R³** and **R⁴** is hydrogen, and the other is halo or CO₂R^a.

15. The compound of any one of claims 1-14, wherein one of **R³** and **R⁴** is hydrogen, and the other is halo (e.g., Br).

16. The compound of any one of claims 1-14, wherein one of **R³** and **R⁴** is hydrogen, and the other is CO₂R^a.

17. The compound of claim 16, wherein **R^a** is C₁₋₆ alkyl optionally substituted with -OH, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -N(H)(C(=O)C₁₋₃ alkyl), or cyano.

18. The compound of claim 16 or 17, wherein **R^a** is unsubstituted C₁₋₆ alkyl.

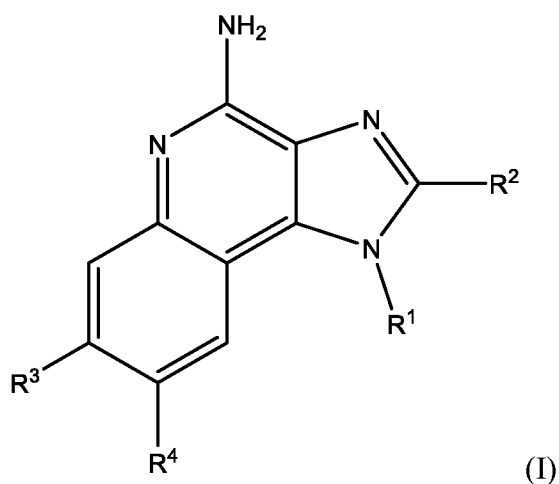
19. The compound of any one of claims 16-18, wherein **R^a** is CH₃ or CH₂CH₃.

20. The compound of any one of claims 1-12, wherein \mathbf{R}^3 is a substituent other than hydrogen, and \mathbf{R}^4 is hydrogen.
21. The compound of any one of claims 1-12 and 20, wherein \mathbf{R}^3 is halo or $\text{CO}_2\mathbf{R}^a$, and \mathbf{R}^4 is hydrogen.
22. The compound of any one of claims 1-12, 20, and 21, wherein \mathbf{R}^3 is halo (e.g., Br), and \mathbf{R}^4 is hydrogen.
23. The compound of any one of claims 1-12, 20, and 21, wherein \mathbf{R}^3 is $\text{CO}_2\mathbf{R}^a$, and \mathbf{R}^4 is hydrogen.
24. The compound of claim 23, wherein \mathbf{R}^a is C_{1-6} alkyl optionally substituted with $-\text{OH}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-3}$ alkyl), $-\text{N}(\text{C}_{1-3}$ alkyl) $_2$, $-\text{N}(\text{H})(\text{C}(=\text{O})\text{C}_{1-3}$ alkyl), or cyano.
25. The compound of claim 23 or 24, wherein \mathbf{R}^a is unsubstituted C_{1-6} alkyl.
26. The compound of any one of claims 23-25, wherein \mathbf{R}^a is CH_3 or CH_2CH_3 .
27. The compound of any one of claims 1 and 3-12, wherein \mathbf{R}^3 is hydrogen, and \mathbf{R}^4 is hydrogen.
28. The compound of claim 1, wherein:
 \mathbf{R}^2 is unsubstituted, unbranched C_{1-6} alkyl; and
 \mathbf{R}^3 and \mathbf{R}^4 are each independently selected from the group consisting of:
(i) hydrogen;
(ii) halo; and
(iv) $\text{CO}_2\mathbf{R}^a$.

29. The compound of claim 28, wherein one of R^3 and R^4 is other than hydrogen.
30. The compound of claim 28 or 29, wherein R^2 is *n*-butyl.
31. The compound of claim 1, wherein:
 R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:
- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
 - heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; and
- R^3 and R^4 are each independently selected from the group consisting of:
- (i) hydrogen;
 - (ii) halo; and
 - (iv) CO₂R^a.
32. The compound of claim 31, wherein one of R^3 and R^4 is other than hydrogen.
33. The compound of claim 31 or 32, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O or S.
34. The compound of any one of claims 31-33, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O.
35. The compound of any one of claims 31-34, wherein R^2 is heteroalkyl, which includes from 3-5 chain atoms, wherein 1 internal chain atom is O.

36. The compound of any one of claims 31-35, wherein R^2 is $-CH_2OCH_2CH_3$.
37. The compound any one of claims 28-36, wherein one of R^3 and R^4 (e.g., R^4) is hydrogen, and the other (e.g., R^3) is a substituent other than hydrogen.
38. The compound any one of claims 28-37, wherein one of R^3 and R^4 (e.g., R^4) is hydrogen, and the other (e.g., R^3) is halo or CO_2R^a .
39. The compound any one of claims 28-38, wherein one of R^3 and R^4 (e.g., R^4) is hydrogen, and the other (e.g., R^3) is halo (e.g., Br).
40. The compound any one of claims 28-38, wherein one of R^3 and R^4 (e.g., R^4) is hydrogen, and the other (e.g., R^3) is CO_2R^a .
41. The compound of claim 40, wherein R^a is C_{1-6} alkyl optionally substituted with $-OH$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl) $_2$, $-N(H)(C(=O)C_{1-3}$ alkyl), or cyano.
42. The compound of claim 41 or 42, wherein R^a is unsubstituted C_{1-6} alkyl.
43. The compound of any one of claims 40-42, wherein R^a is CH_3 or CH_2CH_3 .
44. The compound of any one of claims 28, 30, 31, 33-43, wherein R^3 is hydrogen, and R^4 is hydrogen.
45. The compound of claim 1, wherein the compound is selected from the compounds delineated in Table 1.

46. A compound having formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

R¹ is:

(i) (C₁₋₃ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 **R^a**;

or

(ii) (C₁₋₃ alkylene)heteroaryl including from 5-6 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, and wherein the heteroaryl is optionally substituted with from 1-3 **R^a**;

R² is:

(i) hydrogen;

(ii) unsubstituted, unbranched C₁₋₆ alkyl;

(iii) C₁₋₆ haloalkyl; or

(iv) heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

R^3 and R^4 are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo;
- (iii) cyano;
- (iv) CO_2R^b ;
- (v) $CONR^cR^d$;
- (vi) C_{1-4} alkyl;
- (vii) C_{1-4} haloalkyl;
- (viii) C_{1-4} alkoxy; and
- (ix) C_{1-4} haloalkoxy;

each occurrence of R^a is independently selected from the group consisting of:

- (i) halo;
- (ii) cyano;
- (iii) C_{1-6} alkyl optionally substituted with from 1-2 substituents independently selected from -OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $-CO_2R^b$, $-CONR^cR^d$, cyano, and $-NR^cR^d$;
- (iv) C_{2-6} alkenyl;
- (v) C_{2-6} alkynyl;
- (vi) C_{1-4} haloalkyl;
- (vii) C_{1-4} alkoxy;
- (viii) C_{1-4} haloalkoxy;
- (ix) $-(C_{0-3}$ alkylene)- C_{3-6} cycloalkyl optionally substituted with from 1-4 independently selected C_{1-4} alkyl;
- (x) $-(C_{0-3}$ alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected C_{1-4} alkyl;
- (xi) $-(C_{0-3}$ alkylene)-phenyl optionally substituted with from 1-3 R^e ;

(xii) $-(C_{0-3} \text{ alkylene})\text{-heteroaryl}$ including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heteroaryl is optionally substituted with from 1-3 R^e ;

(xiii) $-S(O)_{1-2}(R^h)$; and

(xiv) $-NR^cR^d$;

R^b is:

(i) H;

(ii) C_{1-6} alkyl optionally substituted with from 1-2 substituents independently selected from $-OH$, $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, $-N(C_{1-3} \text{ alkyl})_2$, $-N(H)(C(=O)C_{1-3} \text{ alkyl})$, or cyano;

(iii) C_{3-6} cycloalkyl optionally substituted with from 1-4 substituents independently selected from C_{1-6} alkyl, C_{1-4} haloalkyl, F, Cl, Br, $-OH$, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; or

(iv) benzyl, wherein the phenyl portion is optionally substituted with from 1-4 substituents independently selected from C_{1-6} alkyl, C_{1-4} haloalkyl, F, Cl, Br, $-OH$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, cyano, $-CO_2(C_{1-6} \text{ alkyl})$; $-CONR^fR^g$, and $-NR^fR^g$;

each occurrence of R^c and R^d is independently selected from the group consisting of: H, C_{1-4} alkyl, $-C(O)(C_{1-4} \text{ alkyl})$, $-C(O)O(C_{1-4} \text{ alkyl})$, $-S(O)_{1-2}(R^h)$, $-C(O)NR^fR^g$, $-OH$, and C_{1-4} alkoxy; or R^c and R^d , together with the nitrogen atom to which each is attached forms heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of $N(R^j)$, O, and S, and wherein the heterocyclyl is optionally further substituted with from 1-4 R^k ,

each occurrence of R^e is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-4} haloalkyl, F, Cl, Br, $-OH$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, cyano, CO_2R^b ; $-CONR^fR^g$, and $-NR^fR^g$;

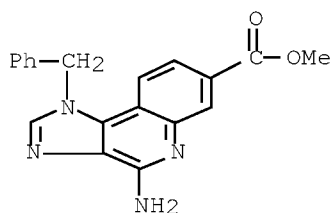
each occurrence of R^f and R^g is independently selected from the group consisting of: H and C_{1-4} alkyl;

each occurrence of R^h is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, phenyl optionally substituted with from 1-3 R^e , and heteroaryl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heteroaryl is optionally substituted with from 1-3 R^e ;

each occurrence of R^j is independently selected from the group consisting of: H, C_{1-4} alkyl, $-C(O)(C_{1-4}$ alkyl), $-C(O)O(C_{1-4}$ alkyl), $-C(O)NR^fR^g$, $-S(O)_{1-2}R^h$, $-OH$, and C_{1-4} alkoxy; and

each occurrence of R^k is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-4} haloalkyl, F, $-OH$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, CO_2R^b ; $-CONR^fR^g$, and $-NR^fR^g$; and

provided that the compound cannot be:



47. The compound of claim 46, wherein one of R^3 and R^4 is other than hydrogen.

48. The compound of claim 46 or 47, wherein R^2 is:

- (ii) unsubstituted, unbranched C_{1-6} alkyl;
- (iii) C_{1-6} haloalkyl; or

(iv) heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy.

49. The compound of claim 46 or 47, wherein **R**² is hydrogen.

50. The compound of any one of claims 46-48, wherein **R**² is unsubstituted, unbranched C₁₋₆ alkyl.

51. The compound of claim 50, wherein **R**² is *n*-butyl.

52. The compound of any one of claims 46-48, wherein **R**² is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy.

53. The compound of claim 52, wherein **R**² is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O or S.

54. The compound of claim 53, wherein **R**² is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O.

55. The compound of claim 54, wherein **R**² is heteroalkyl, which includes from 3-5 chain atoms, wherein 1 internal chain atom is O.

56. The compound of claim 55, wherein R^2 is $-CH_2OCH_2CH_3$.
57. The compound of any one of claims 47-56, wherein R^1 is $(C_{1-3}$ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 R^d .
58. The compound of claim 57, wherein R^1 is $(C_{1-3}$ alkylene)phenyl, wherein the phenyl is optionally substituted with from 1-3 R^d .
59. The compound of claim 57, wherein R^1 is $(C_{1-3}$ alkylene)aryl, wherein the aryl is substituted with from 1-3 R^d .
60. The compound of claim 59, wherein R^1 is $(C_{1-3}$ alkylene)phenyl, wherein the phenyl is substituted with from 1-3 R^d .
61. The compound of claim 60, wherein R^1 is $(C_{1-3}$ alkylene)phenyl, wherein the phenyl is substituted with 1 R^d .
62. The compound any one of claims 57-61, wherein R^d , or at least one R^d is C_{1-6} alkyl optionally substituted with from 1-2 substituents independently selected from -OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $-CO_2R^a$, $-CONR^bR^c$, cyano, and $-NR^bR^c$.
63. The compound any one of claims 57-62, wherein R^d , or at least one R^d is C_{1-6} alkyl substituted with from 1-2 substituents independently selected from -OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $-CO_2R^a$, $-CONR^bR^c$, cyano, and $-NR^bR^c$.
64. The compound of any one of claims 46-63, wherein R^3 and R^4 are each independently selected from the group consisting of:
- (i) hydrogen;
 - (ii) halo;
 - (iii) cyano;

- (iv) CO₂R^a; and
- (v) CONR^bR^c.

65. The compound of any one of claims 46-64, wherein **R**³ and **R**⁴ are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo; and
- (iv) CO₂R^a.

66. The compound of any one of claims 46-65, wherein one of **R**³ and **R**⁴ is hydrogen, and the other is a substituent other than hydrogen.

67. The compound of any one of claims 46-66, wherein one of **R**³ and **R**⁴ is hydrogen, and the other is halo or CO₂R^a.

68. The compound of any one of claims 46-67, wherein one of **R**³ and **R**⁴ is hydrogen, and the other is halo (e.g., Br).

69. The compound of any one of claims 46-67, wherein one of **R**³ and **R**⁴ is hydrogen, and the other is CO₂R^a.

70. The compound of claim 69, wherein **R**^a is C₁₋₆ alkyl optionally substituted with -OH, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -N(H)(C(=O)C₁₋₃ alkyl), or cyano.

71. The compound of claim 69 or 70, wherein **R**^a is unsubstituted C₁₋₆ alkyl.

72. The compound of any one of claims 69-71, wherein **R**^a is CH₃ or CH₂CH₃.

73. The compound of any one of claims 46-63, wherein **R**³ is a substituent other than hydrogen, and **R**⁴ is hydrogen.

74. The compound of any one of claims 46-63 and 73, wherein \mathbf{R}^3 is halo or $\text{CO}_2\mathbf{R}^a$, and \mathbf{R}^4 is hydrogen.

75. The compound of any one of claims 46-73, 73, and 74, wherein \mathbf{R}^3 is halo (e.g., Br), and \mathbf{R}^4 is hydrogen.

76. The compound of any one of claims 46-73, 73, and 74, wherein \mathbf{R}^3 is $\text{CO}_2\mathbf{R}^a$, and \mathbf{R}^4 is hydrogen.

77. The compound of claim 76, wherein \mathbf{R}^a is C_{1-6} alkyl optionally substituted with $-\text{OH}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-3}$ alkyl), $-\text{N}(\text{C}_{1-3}$ alkyl) $_2$, $-\text{N}(\text{H})(\text{C}(=\text{O})\text{C}_{1-3}$ alkyl), or cyano.

78. The compound of claim 76 or 77, wherein \mathbf{R}^a is unsubstituted C_{1-6} alkyl.

79. The compound of any one of claims 76-78, wherein \mathbf{R}^a is CH_3 or CH_2CH_3 .

80. The compound of any one of claims 46 and 48-65, wherein \mathbf{R}^3 is hydrogen, and \mathbf{R}^4 is hydrogen.

81. The compound of claim 46, wherein:

\mathbf{R}^2 is unsubstituted, unbranched C_{1-6} alkyl; and

\mathbf{R}^3 and \mathbf{R}^4 are each independently selected from the group consisting of:

(i) hydrogen;

(ii) halo; and

(iv) $\text{CO}_2\mathbf{R}^a$.

82. The compound of claim 46, wherein:

\mathbf{R}^1 is $(\text{C}_{1-3}$ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 \mathbf{R}^a ;

\mathbf{R}^2 is unsubstituted, unbranched C_{1-6} alkyl; and

R³ and **R**⁴ are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo; and
- (iv) CO₂R^a.

83. The compound of claim 81 or 82, wherein one of **R**³ and **R**⁴ is other than hydrogen.

84. The compound of any one of claims 81-83, wherein **R**¹ is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 **R**^a.

85. The compound of any one of claims 81-84, wherein **R**² is *n*-butyl.

86. The compound of claim 46, wherein:

R² is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; and

R³ and **R**⁴ are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo; and
- (iv) CO₂R^a.

87. The compound of claim 46, wherein:

R¹ is (C₁₋₃ alkylene)aryl, wherein the aryl is optionally substituted with from 1-3 **R**^a;

R² is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; and

R³ and **R⁴** are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo; and
- (iv) CO₂R^a.

88. The compound of claim 86 or 87, wherein one of **R³** and **R⁴** is other than hydrogen.

89. The compound of any one of claims 86-88, wherein **R¹** is (C₁₋₃ alkylene)aryl, wherein the aryl is substituted with from 1-3 **R^a**.

90. The compound of any one of claims 86-89, wherein **R²** is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O or S.

91. The compound of any one of claims 86-90, wherein **R²** is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O.

92. The compound of any one of claims 86-91, wherein **R²** is heteroalkyl, which includes from 3-5 chain atoms, wherein 1 internal chain atom is O.

93. The compound of any one of claims 86-92, wherein **R²** is -CH₂OCH₂CH₃.

94. The compound any one of claims 81-93, wherein one of \mathbf{R}^3 and \mathbf{R}^4 (e.g., \mathbf{R}^4) is hydrogen, and the other (e.g., \mathbf{R}^3) is a substituent other than hydrogen.

95. The compound any one of claims 81-94, wherein one of \mathbf{R}^3 and \mathbf{R}^4 (e.g., \mathbf{R}^4) is hydrogen, and the other (e.g., \mathbf{R}^3) is halo or $\text{CO}_2\mathbf{R}^a$.

96. The compound any one of claims 81-95, wherein one of \mathbf{R}^3 and \mathbf{R}^4 (e.g., \mathbf{R}^4) is hydrogen, and the other (e.g., \mathbf{R}^3) is halo (e.g., Br).

97. The compound any one of claims 81-95, wherein one of \mathbf{R}^3 and \mathbf{R}^4 (e.g., \mathbf{R}^4) is hydrogen, and the other (e.g., \mathbf{R}^3) is $\text{CO}_2\mathbf{R}^a$.

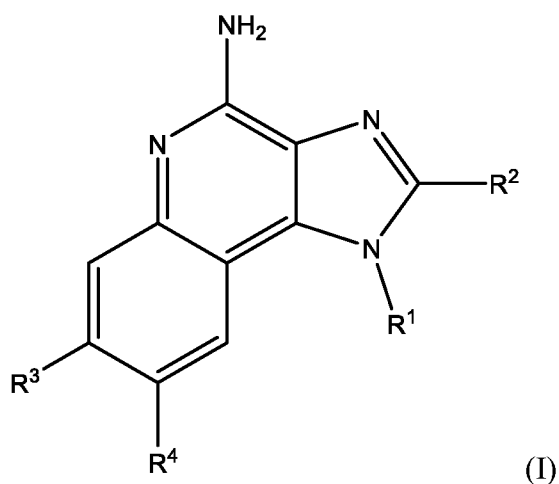
98. The compound of claim 97, wherein \mathbf{R}^a is C_{1-6} alkyl optionally substituted with $-\text{OH}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-3} \text{ alkyl})$, $-\text{N}(\text{C}_{1-3} \text{ alkyl})_2$, $-\text{N}(\text{H})(\text{C}(=\text{O})\text{C}_{1-3} \text{ alkyl})$, or cyano.

99. The compound of claim 97 or 98, wherein \mathbf{R}^a is unsubstituted C_{1-6} alkyl.

100. The compound of any one of claims 97-99, wherein \mathbf{R}^a is CH_3 or CH_2CH_3 .

101. The compound of any one of claims 81, 82, 84-87, and 89-93, wherein \mathbf{R}^3 is hydrogen, and \mathbf{R}^4 is hydrogen.

102. A compound having formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

R¹ is **X-R⁵**, wherein **X** is unbranched C₂₋₆ alkylene or -O(unbranched C₂₋₆ alkylene)-, and **R⁵** is hydrogen, -OH, C₁₋₄ alkoxy, -C₁₋₄ alkoxy, CO₂R^a, -CONR^bR^c, cyano, or -NR^bR^c;

R² is:

- (i) hydrogen;
- (ii) unsubstituted, unbranched C₁₋₆ alkyl;
- (iii) C₁₋₆ haloalkyl; or
- (iv) heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:
 - when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
 - heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

R³ and **R⁴** are each independently selected from the group consisting of:

- (i) hydrogen;

- (ii) halo;
- (iii) cyano;
- (iv) CO₂R^a;
- (v) CONR^bR^c;
- (vi) C₁₋₄ alkyl;
- (vii) C₁₋₄ haloalkyl;
- (viii) C₁₋₄ alkoxy; and
- (ix) C₁₋₄ haloalkoxy;

R^a is:

- (i) H;
- (ii) C₁₋₆ alkyl optionally substituted with from 1-2 substituents independently selected from -OH, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -N(H)(C(=O)C₁₋₃ alkyl), or cyano;
- (iii) C₃₋₆ cycloalkyl optionally substituted with from 1-4 substituents independently selected from C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; or
- (iv) benzyl, wherein the phenyl portion is optionally substituted with from 1-4 substituents independently selected from C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, cyano, CO₂(C₁₋₆ alkyl); -CONR^dR^e, and -NR^dR^e;

each occurrence of **R^b** and **R^c** is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -S(O)₁₋₂(**R^f**), -C(O)NR^dR^e, -OH, and C₁₋₄ alkoxy; or **R^b** and **R^c**, together with the nitrogen atom to which each is attached forms heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R^g**), O, and S, and wherein the heterocyclyl is optionally further substituted with from 1-4 **R^h**,

each occurrence of **R^d** and **R^e** is independently selected from the group consisting of: H and C₁₋₄ alkyl;

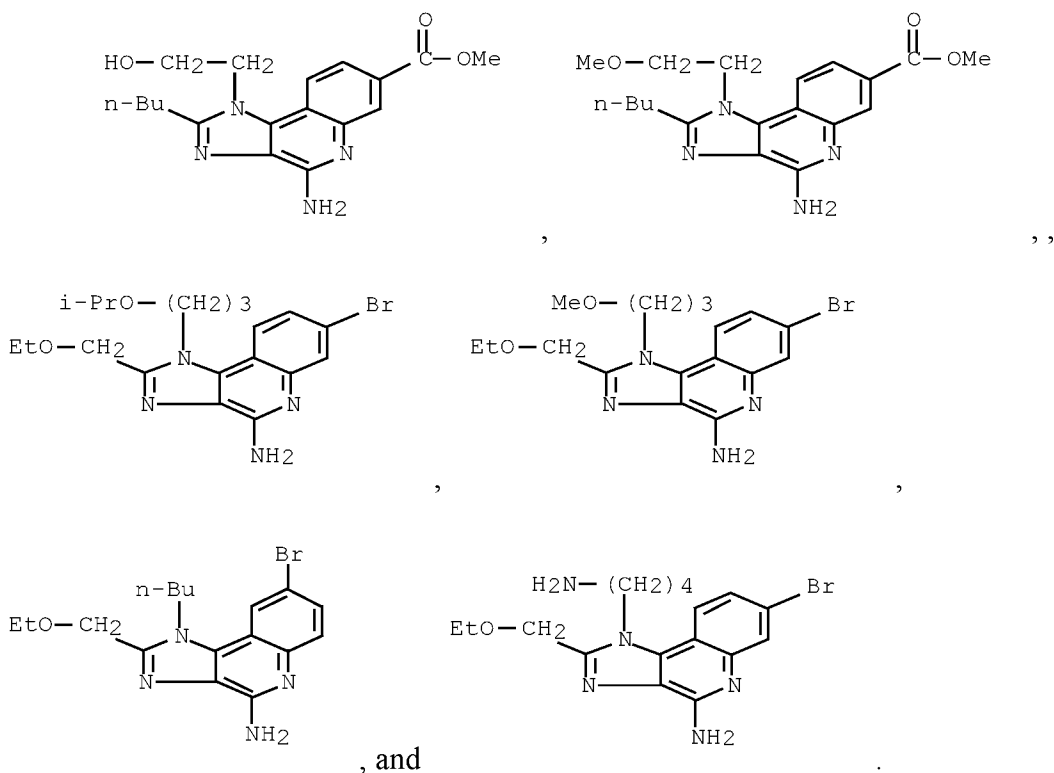
each occurrence of R^f is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, phenyl optionally substituted with from 1-3 R^m , and heteroaryl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of nitrogen, oxygen and sulfur, wherein the heteroaryl is optionally substituted with from 1-3 R^m ;

each occurrence of R^g is independently selected from the group consisting of: H, C₁₋₄ alkyl, -C(O)(C₁₋₄ alkyl), -C(O)O(C₁₋₄ alkyl), -C(O)NR^jR^k, -S(O)₁₋₂R^h, -OH, and C₁₋₄ alkoxy;

each occurrence of R^h is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, CO₂R^a, -CONR^jR^k, and -NR^jR^k; and

each occurrence of R^m is independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₄ haloalkyl, F, Cl, Br, -OH, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, cyano, CO₂R^a, -CONR^dR^e, and -NR^dR^e; and

provided the compound is not:



103. The compound of claim 102, wherein one of **R**³ and **R**⁴ is other than hydrogen.

104. The compound of claim 102 or 103, **X** is -O(straight chain C₂₋₆ alkylene)-.

105. The compound of any one of claims 102-104, wherein **R**² is hydrogen.

106. The compound of any one of claims 102-104, wherein **R**² is unsubstituted, unbranched C₁₋₆ alkyl.

107. The compound of claim 106, wherein **R**² is *n*-butyl.

108. The compound of any one of claims 102-104, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy.

109. The compound of claim 108, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O or S.

110. The compound of claim 109, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O.

111. The compound of claim 110, wherein R^2 is heteroalkyl, which includes from 3-5 chain atoms, wherein 1 internal chain atom is O.

112. The compound of claim 55, wherein R^2 is $-CH_2OCH_2CH_3$.

113. The compound of any one of claims 102, 103, and 105-112, wherein X is unbranched C₂₋₆ alkylene.

114. The compound of any one of claims 102-113, wherein R^5 is -OH, C₁₋₄ alkoxy, -C₁₋₄ haloalkoxy, CO₂R^a; or -NR^bR^c.

115. The compound of any one of claims 102-114, wherein R^5 is -OH, C₁₋₄ alkoxy, -C₁₋₄ haloalkoxy, or CO₂R^a.

116. The compound of any one of claims 102-115, wherein R^5 is C₁₋₄ alkoxy or -C₁₋₄ haloalkoxy (e.g., C₁₋₄ alkoxy, e.g., OCH₃).

117. The compound of any one of claims 102-114, wherein \mathbf{R}^5 is $\text{CO}_2\mathbf{R}^a$.
118. The compound of claim 117, wherein \mathbf{R}^a is C_{1-6} alkyl optionally substituted with $-\text{OH}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-3}$ alkyl), $-\text{N}(\text{C}_{1-3}$ alkyl) $_2$, $-\text{N}(\text{H})(\text{C}(=\text{O})\text{C}_{1-3}$ alkyl), or cyano.
119. The compound of claim 92 or 93, wherein \mathbf{R}^a is unsubstituted C_{1-6} alkyl.
120. The compound of any one of claims 117-119, wherein \mathbf{R}^a is CH_3 or CH_2CH_3 .
121. The compound of any one of claims 102-114, wherein \mathbf{R}^5 is $-\text{NR}^b\mathbf{R}^c$.
122. The compound of claim 121, wherein each occurrence of \mathbf{R}^b and \mathbf{R}^c is independently selected from the group consisting of: H, C_{1-4} alkyl, $-\text{C}(\text{O})(\text{C}_{1-4}$ alkyl), $-\text{C}(\text{O})\text{O}(\text{C}_{1-4}$ alkyl), $-\text{S}(\text{O})_{1-2}(\mathbf{R}^h)$, $-\text{C}(\text{O})\text{NR}^j\mathbf{R}^k$, $-\text{OH}$, and C_{1-4} alkoxy.
123. The compound of claim 121 or 122, wherein each occurrence of \mathbf{R}^b and \mathbf{R}^c is independently selected from the group consisting of: H, C_{1-4} alkyl, $-\text{C}(\text{O})(\text{C}_{1-4}$ alkyl), $-\text{C}(\text{O})\text{O}(\text{C}_{1-4}$ alkyl), $-\text{S}(\text{O})_{1-2}(\mathbf{R}^h)$, and $-\text{C}(\text{O})\text{NR}^j\mathbf{R}^k$.
124. The compound of any one of claims 121-123, wherein each occurrence of \mathbf{R}^b and \mathbf{R}^c is independently selected from the group consisting of: H, C_{1-4} alkyl, and $-\text{C}(\text{O})(\text{C}_{1-4}$ alkyl).
125. The compound of any one of claims 121-124, wherein each occurrence of \mathbf{R}^b and \mathbf{R}^c is independently selected from the group consisting of: H and C_{1-4} alkyl.
126. The compound of claim 125, wherein \mathbf{R}^6 is $-\text{NH}_2$, $-\text{N}(\text{H})(\text{C}_{1-4}$ alkyl) (e.g., $-\text{NHCH}_3$) or $-\text{N}(\text{C}_{1-4}$ alkyl) $_2$ (e.g., $-\text{N}(\text{CH}_3)_2$).

127. The compound of any one of claims 102-126, wherein R^3 and R^4 are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo;
- (iii) cyano;
- (iv) CO_2R^a ; and
- (v) $CONR^bR^c$.

128. The compound of any one of claims 102-127, wherein R^3 and R^4 are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo; and
- (iv) CO_2R^a .

129. The compound of any one of claims 102-128, wherein one of R^3 and R^4 is hydrogen, and the other is a substituent other than hydrogen.

130. The compound of any one of claims 102-129, wherein one of R^3 and R^4 is hydrogen, and the other is halo or CO_2R^a .

131. The compound of any one of claims 102-130, wherein one of R^3 and R^4 is hydrogen, and the other is halo (e.g., Br).

132. The compound of any one of claims 102-131, wherein one of R^3 and R^4 is hydrogen, and the other is CO_2R^a .

133. The compound of claim 132, wherein R^a is C_{1-6} alkyl optionally substituted with $-OH$, $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, $-N(C_{1-3} \text{ alkyl})_2$, $-N(H)(C(=O)C_{1-3} \text{ alkyl})$, or cyano.

134. The compound of claim 132 or 133, wherein R^a is unsubstituted C_{1-6} alkyl.
135. The compound of any one of claims 132-134, wherein R^a is CH_3 or CH_2CH_3 .
136. The compound of any one of claims 102-126, wherein R^3 is a substituent other than hydrogen, and R^4 is hydrogen.
137. The compound of any one of claims 102-126 and 136, wherein R^3 is halo or CO_2R^a , and R^4 is hydrogen.
138. The compound of any one of claims 102-126, 136, and 137, wherein R^3 is halo (e.g., Br), and R^4 is hydrogen.
139. The compound of any one of claims 102-126, 136, and 137, wherein R^3 is CO_2R^a , and R^4 is hydrogen.
140. The compound of claim 139, wherein R^a is C_{1-6} alkyl optionally substituted with $-OH$, $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, $-N(C_{1-3} \text{ alkyl})_2$, $-N(H)(C(=O)C_{1-3} \text{ alkyl})$, or cyano.
141. The compound of claim 139 or 140, wherein R^a is unsubstituted C_{1-6} alkyl.
142. The compound of any one of claims 139-141, wherein R^a is CH_3 or CH_2CH_3 .
143. The compound of any one of claims 102 and 48-65, wherein R^3 is hydrogen, and R^4 is hydrogen.
144. The compound of claim 102, wherein:

R² is unsubstituted, unbranched C₁₋₆ alkyl; and

R³ and **R**⁴ are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo; and
- (iv) CO₂R^a.

145. The compound of claim 144, wherein one of **R**³ and **R**⁴ is other than hydrogen.

146. The compound of claim 144 or 145, wherein **R**² is *n*-butyl.

147. The compound of claim 102, wherein:

R² is heteroalkyl, which includes from 3-8 chain atoms, wherein from 1-2 internal chain atoms are heteroatoms that are independently selected from O and S; wherein:

- when two heteroatoms are present in the chain, the two heteroatoms must be separated by at least one chain carbon atom; and
- heteroalkyl is optionally substituted with from 1-4 substituents independently selected from F, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy; and

R³ and **R**⁴ are each independently selected from the group consisting of:

- (i) hydrogen;
- (ii) halo; and
- (iv) CO₂R^a.

148. The compound of claim 147, wherein one of **R**³ and **R**⁴ is other than hydrogen.

149. The compound of claim 147 or 148, wherein **R**² is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O or S.

150. The compound of any one of claims 147-149, wherein R^2 is heteroalkyl, which includes from 3-8 chain atoms, wherein 1 internal chain atom is O.

151. The compound of any one of claims 147-150, wherein R^2 is heteroalkyl, which includes from 3-5 chain atoms, wherein 1 internal chain atom is O.

152. The compound of any one of claims 147-151, wherein R^2 is –
CH₂OCH₂CH₃.

153. The compound any one of claims 144-152, wherein one of R^3 and R^4 (e.g., R^4) is hydrogen, and the other (e.g., R^3) is a substituent other than hydrogen.

154. The compound any one of claims 144-153, wherein one of R^3 and R^4 (e.g., R^4) is hydrogen, and the other (e.g., R^3) is halo or CO₂R^a.

155. The compound any one of claims 144-154, wherein one of R^3 and R^4 (e.g., R^4) is hydrogen, and the other (e.g., R^3) is halo (e.g., Br).

156. The compound any one of claims 144-154, wherein one of R^3 and R^4 (e.g., R^4) is hydrogen, and the other (e.g., R^3) is CO₂R^a.

157. The compound of claim 156, wherein R^a is C₁₋₆ alkyl optionally substituted with –OH, –NH₂, –NH(C₁₋₃ alkyl), –N(C₁₋₃ alkyl)₂, –N(H)(C(=O)C₁₋₃ alkyl), or cyano.

158. The compound of claim 157 or 158, wherein R^a is unsubstituted C₁₋₆ alkyl.

159. The compound of any one of claims 156-158, wherein R^a is CH₃ or CH₂CH₃.

160. The compound of any one of claims 144, 146, 147, and 148-159, wherein R^3 is hydrogen, and R^3 is hydrogen.

161. The compound of claim 46 or 102, wherein the compound is selected from the compounds delineated in Table 1.

162. A pharmaceutical composition comprising a compound or salt as claimed in any one of claims 1-161 and one or more pharmaceutically acceptable excipients.

163. A method for modulating NLRP3 and TLR7 and/or TLR8 activity, the method comprising contacting NLRP3 and TLR7 and/or TLR8 with a compound as claimed in any one of claims 1-161.

164. The method of claim 163, wherein the modulating comprises agonizing NLRP3 and TLR7 and/or TLR8.

165. The method of claim 163, wherein the modulating comprises partially agonizing NLRP3 and TLR7 and/or TLR8.

166. The method of any one of claims 163-165, which is carried out *in vitro*.

167. The method of any one of claims 163-165, which is carried out *in vivo*.

168. A method of treating cancer, comprising administering to a subject in need of such treatment an effective amount of a compound as claimed in any one of claims 1-161, or a pharmaceutical composition as claimed in claim 162.

169. The method of claim 168, wherein the cancer is selected from the group consisting of acute myeloid leukemia, adrenocortical carcinoma, Kaposi sarcoma, lymphoma, anal cancer, appendix cancer, teratoid/rhabdoid tumor, basal cell carcinoma,

bile duct cancer, bladder cancer, bone cancer, brain cancer, breast cancer, bronchial tumor, carcinoid tumor, cardiac tumor, cervical cancer, chordoma, chronic lymphocytic leukemia, chronic myeloproliferative neoplasm, colon cancer, colorectal cancer, craniopharyngioma, bile duct cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, eye cancer, fallopian tube cancer, gallbladder cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, germ cell tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hypopharyngeal cancer, pancreatic cancer, kidney cancer, laryngeal cancer, chronic myelogenous leukemia, lip and oral cavity cancer, lung cancer, melanoma, Merkel cell carcinoma, mesothelioma, mouth cancer, oral cancer, osteosarcoma, ovarian cancer, penile cancer, pharyngeal cancer, prostate cancer, rectal cancer, salivary gland cancer, skin cancer, small intestine cancer, soft tissue sarcoma, testicular cancer, throat cancer, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, and vulvar cancer.

170. The method of claim 168 or 169, wherein the cancer is a refractory cancer.

171. The method of claim 170, wherein the compound is administered in combination with one or more additional cancer therapies.

172. The method of claim 171, wherein the one or more additional cancer therapies comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy, or a combination thereof.

173. The method of claim 172, wherein chemotherapy comprises administering one or more additional chemotherapeutic agents.

174. The method of claim 173, wherein the one or more additional chemotherapeutic agents is selected from an alkylating agent (e.g., cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin); an anti-metabolite (e.g., azathioprine and/or mercaptopurine); a terpenoid (e.g., a vinca

alkaloid and/or a taxane; e.g., Vincristine, Vinblastine, Vinorelbine and/or Vindesine Taxol, Paclitaxel and/or Docetaxel); a topoisomerase (e.g., a type I topoisomerase and/or a type 2 topoisomerase; e.g., camptothecins, such as irinotecan and/or topotecan; amsacrine, etoposide, etoposide phosphate and/or teniposide); a cytotoxic antibiotic (e.g., actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and/or mitomycin); a hormone (e.g., a lutenizing hormone releasing hormone agonist; e.g., leuprolidine, goserelin, triptorelin, histrelin, bicalutamide, flutamide and/or nilutamide); an antibody (e.g., Abciximab, Adalimumab, Alemtuzumab, Atlizumab, Basiliximab, Belimumab, Bevacizumab, Bretuximab vedotin, Canakinumab, Cetuximab, Ceertolizumab pegol, Daclizumab, Denosumab, Eculizumab, Efalizumab, Gemtuzumab, Golimumab, Golimumab, Ibritumomab tiuxetan, Infliximab, Ipilimumab, Muromonab-CD3, Natalizumab, Ofatumumab, Omalizumab, Palivizumab, Panitumuab, Ranibizumab, Rituximab, Tocilizumab, Tositumomab and/or Trastuzumab); an anti-angiogenic agent; a cytokine; a thrombotic agent; a growth inhibitory agent; an anti-helminthic agent; and an immune checkpoint inhibitor that targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70-CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM – LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2–TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA–CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or PD-L1) and other immunomodulatory agents, such as interleukin-2 (IL-2), indoleamine

2,3-dioxygenase (IDO), IL-10, transforming growth factor- β (TGF β), CD39, CD73 Adenosine-CD39-CD73, and CXCR4-CXCL12.

175. The method of any one of claims 168-174, wherein the compound is administered intratumorally.

176. The method of any one of claims 168-174, wherein the compound is administered systemically.

177. The method of any one of claims 168-176, wherein the method further comprises identifying the subject.

178. The method of any one of claims 168-177, wherein the subject is a human.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P35/00 A61P37/00 A61P31/00
ADD.
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)
C07D
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A A X	<p>WO 2016/055812 A1 (ISIS INNOVATION [GB]; US HEALTH [US]) 14 April 2016 (2016-04-14) page 40, formula 7 page 54; compound 15 -----</p> <p>WO 2015/095780 A1 (UNIV KANSAS [US]; DAVID SUNIL ABRAHAM [US]; KOKATLA HARI PRASAD [US];) 25 June 2015 (2015-06-25) page 18, lines 7-8; compound 2 -----</p> <p>WO 02/24225 A1 (GLAXO GROUP LTD [GB]; THOMSEN LINDY LOUISE [GB]; TITE JOHN PHILIP [GB]) 28 March 2002 (2002-03-28) claim 5, formula III page 3, lines 17-20 -----</p> <p style="text-align: center;">-/--</p>	<p>102 1-45, 162-178 1-45, 162-178 1-45, 162-178</p>

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
- "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 24 July 2017	Date of mailing of the international search report 08/08/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Gutke, Hans-Jürgen

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/088924 A1 (TELORMEDIX SA [CH]; LEONI LORENZO [CH]; MAJ ROBERTO [IT]; PATTARINO FR) 12 August 2010 (2010-08-12) Claim 4(a) claim 4b), formula I; 4e), formula IV page 38, lines 3-5 page 54, lines 8-17 page 55, line 5 -----	1-45, 162-178
X	WO 2006/073940 A2 (3M INNOVATIVE PROPERTIES CO [US]; SLADE HERBERT B [US]; GUY CYNTHIA A) 13 July 2006 (2006-07-13) page 19; compound III page 20; compound V page 14, lines 7-8, 18 -----	1-45, 162-178
X	EP 0 145 340 A2 (RIKER LABORATORIES INC [US]) 19 June 1985 (1985-06-19) claims 1, 16 page 52; example 170 -----	46,48, 50, 57-61, 64,65, 81,82, 101, 162-169
X	WO 93/05042 A1 (MINNESOTA MINING & MFG [US]) 18 March 1993 (1993-03-18) claim 1 page 16, lines 22-23 pages 23, 25; examples 14, 18 -----	46,48, 50-56, 64,65, 80,81, 86, 90-93, 101
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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 2006/065280 A2 (3M INNOVATIVE PROPERTIES CO [US]; MOSER WILLIAM H [US]; MOSEMAN JOAN T) 22 June 2006 (2006-06-22)</p> <p>claims 3, 30, 31 page 147; compounds IIIc, IIId</p> <p>-----</p>	<p>46,48, 50-56, 64,65, 80,81, 83,86, 90-93, 97-101, 161-169</p>
X	<p>WO 2007/079086 A1 (3M INNOVATIVE PROPERTIES CO [US]; HAYS DAVID S [US]; KSHIRSAGAR TUSHAR) 12 July 2007 (2007-07-12)</p> <p>claims 2, 38, 39 pages 101-103; compounds IIa, IIb</p> <p>-----</p>	<p>46,48, 50-56, 64,65, 80,81, 86, 90-93, 101, 162-169</p>
X	<p>WO 2013/033345 A1 (UNIV MINNESOTA [US]; FERGUSON DAVID M [US]; OHLFEST JOHN [US]; ALDRICH) 7 March 2013 (2013-03-07)</p> <p>claims 1, 33 claim 25; compounds 514,521,529</p> <p>-----</p>	<p>46,47, 49, 57-67, 69-74, 76-79, 102,104, 106,107, 113-116, 127-130, 132-137, 139-142, 144-146, 153,154, 156-159, 162-178</p>
X	<p>WO 2004/058759 A1 (3M INNOVATIVE PROPERTIES CO [US]) 15 July 2004 (2004-07-15)</p> <p>page 42; compound XXXIV example 493, step D, page 305 page 140, example 157, starting material page 333, part A pages 318-319, part A page 390, part B</p> <p>-----</p>	<p>46-48, 52-68, 73-75, 86-96, 102, 106-114, 121-131, 136-138, 144-155</p>

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 348 462 B1 (GERSTER JOHN F [US] ET AL) 19 February 2002 (2002-02-19) column 37; example 117 -----	102, 108-113, 127,128, 143,160, 162-169
X	WO 2006/091394 A2 (3M INNOVATIVE PROPERTIES CO [US]; RICE MICHAEL J [US]; HARALDSON CHAD) 31 August 2006 (2006-08-31) page 42; compound XV part E; example 1 -----	102,103, 108-116, 127-131, 136-138, 147-155
X	WO 2005/051317 A2 (3M INNOVATIVE PROPERTIES CO [US]; KREPSKI LARRY R [US]; DELLARIA JOSEP) 9 June 2005 (2005-06-09) claims 2, 30 page 119; example 34 -----	102, 108-115, 117-120, 127,128, 147-152, 160, 162-169
X	GERSTER JF ET AL: "Synthesis and structure-activity-relationships of 1H-imidazo[4,5-c]quinolines that induce interferon production", JOURNAL OF MEDICINAL CHEM, AMERICAN CHEMICAL SOCIETY, vol. 48, no. 10, 21 April 2005 (2005-04-21), pages 3481-3491, XP008115095, ISSN: 0022-2623, DOI: 10.1021/JM049211V compounds 2, 22, 23, 25, 28 -----	102,105, 160,162

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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.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
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:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-45(completely); 162-178(partially)

compounds of formula I of claim 1

2. claims: 46-101(completely); 161-178(partially)

compounds of formula I of claim 46

3. claims: 102-160(completely); 161-178(partially)

compounds of formula I of claim 102

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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