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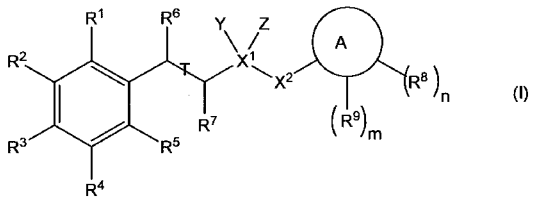

(I)

(57) Abstract: The present invention relates to analogues of anti-fibrotic agents having the formula (I) with the substituents as described within the specification. The present invention also relates to methods for their preparation.

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ANALOGUES OF ANTI-FIBROTIC AGENTS

Field of the invention

The present invention relates to derivatives of the anti-fibrotic drug, Tranilast.

Background of the invention

Fibrosis is a common response to a range of tissue insults that may lead to organ dysfunction. Diseases that are characterised by such pathological fibrosis include hepatic cirrhosis, pulmonary interstitial fibrosis, glomerulonephritis, heart failure (ischaemic and non-ischaemic), diabetic nephropathy, scleroderma, excessive scar tissue post surgery or device insertion, progressive kidney disease, glomerulonephritis, hypertension, heart failure due to ischaemic heart disease, valvular heart disease or hypertensive heart disease and hypertrophic scars. In addition, the elaboration of pathological matrix also has a role in fibroproliferative tumor progression and metastasis. Studies conducted over more than a decade have consistently indicated a major role of TGF-β in organ fibrosis and dysfunction, such that blockade of its expression and action represent an important therapeutic target.

Existing agents for treating fibrosis may have any number of undesirable properties including toxicity, poor solubility or efficacy.

One anti-fibrotic agent is Tranilast (n-[3,4-dimethoxycinnamoyl] anthranilic acid) and is used in Japan for the treatment of fibrotic skin disorders such as keloids and scleroderma. Although the precise mechanisms and mode of action of Tranilast are not completely understood, its ability to inhibit ERK phosphorylation, a major intermediate in the TGF-β signalling pathway, may underlie its antifibrotic effects, with known actions of Tranilast including the inhibition of TGF-β-induced extracellular matrix production in a range of cell types. Tranilast has also been shown to attenuate TGF-β-induced collagen synthesis in cardiac fibroblasts using an experimental model of diabetic cardiac disease.

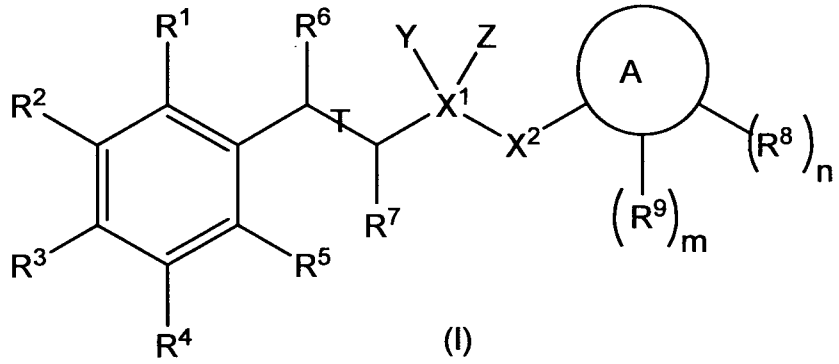
Tranilast has also been shown to reduce inflammation in allergic diseases, such as allergic rhinitis and bronchial asthma, and to have anti-proliferative activity.

However, it has recently been shown that genetic factors in certain patients, specifically the presence of a Gilbert's syndrome UGT1A1 variant, confer susceptibility to Tranilast-induced hyperbilirubinemia. Such hyperbilirubinemia may be associated with inhibition of UGT1A1 by Tranilast *per se* and/or the *in vivo* formation of a Tranilast derivative.

Therefore, it would be desirable to provide further alternatives to existing agents with potential anti-fibrotic, anti-inflammatory and anti-proliferative or anti-neoplastic activity for the treatment or prevention of diseases associated with fibrosis.

Summary of the invention

The present invention provides a compound of Formula (I)



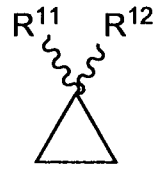
(I)

or a pharmaceutically acceptable drug or prodrug thereof,

wherein;

$X^1(YZ)$ is C=O, $C(F_2)$ or SO_2;

X^2 is NR^{10} or $(CH_2)_p$;

T is a double bond, a triple bond or when T is a single bond, one pair of R^6 and R^7 are fused to form a cyclopropane ring of the formula  ;

A is selected from the group consisting of C_3 to C_{12} cycloalkyl, C_3 to C_{12} cycloalkenyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} heterocycloalkenyl, C_6-C_{18} aryl and C_6 to C_{18} heteroaryl;

R^1, R^4, and R^5 are each independently selected from the group consisting of: H, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl,

optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{13}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}R^{14}$, and acyl;

R^2 and R^3, are each independently selected from the group consisting of: H, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{13}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}R^{14}$ and acyl; or
R^2 and R^3 may be fused to form a 5 or 6 membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring each of which may be optionally substituted;

one pair of R^6 and R^7 are present when T is a double bond but R^6 and R^7 are not present when T is a triple bond, each R^6 and R^7 being independently selected from the group consisting of: H, NO_2, CN, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted C_2-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, optionally substituted C_1-C_{18} heteroaryl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy,

optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{14}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}R^{14}$, and acyl;

R^8 is selected from the group consisting of H, halogen, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{13}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$ and $NR^{13}R^{14}$ and acyl;

R^9 is selected from the group consisting of OH, OR^{13}, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, tetrazol-5-yl, SO_2R^{13}, $SO_2NR^{13}R^{14}$ and $CONHOR^{13}$;

R^{10} is selected from the group consisting of H, a N-protecting group, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} heterocycloalkyl, optionally substituted C_1-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

R^{11} and R^{12} are independently selected from the group consisting of H, halogen, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted C_2-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, optionally substituted C_1-C_{18} heteroaryl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally

substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{13}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}R^{14}$, and acyl;

each R^{13}, R^{14}, R^{15} are each independently selected from the group consisting of H, -OH, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} heterocycloalkyl, optionally substituted C_1-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

n is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

m is an integer selected from the group consisting of 1, 2, 3, and 4;

m + n is an integer selected from the group consisting of 1, 2, 3, 4, and 5; and

p is an integer selected from the group consisting of 0, 1, 2, 3, 4, and 5;

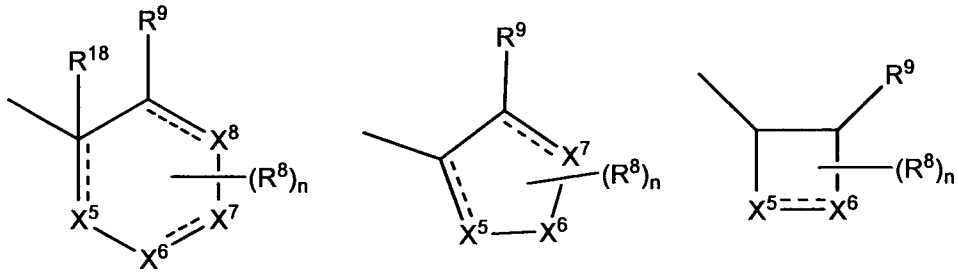
and when $X^1(YZ)$ is $C(F_2)$ or SO_2; or
when T is a cyclopropane ring as defined above; or
when R^1 and R^5 are H and T is a double bond; or
when X^2 is $(CH_2)_p$ and p is 0 or 1; or
when A is selected from the group consisting of C_3 to C_{12} cycloalkyl, preferably C_4 to C_6 cycloalkyl, C_1 to C_{12} heterocycloalkenyl, and C_6 to C_{18} heteroaryl;
then R^2 and R^3 may also be independently selected from $-X^3$-R^{16} or $-X^4$-R^{17};

wherein X^3 and X^4 may be the same or different and are selected from the group consisting of a bond C, O, N and S; and

R^{16} and R^{17} may be the same or different and are selected from the group consisting of H, NHR^{13}, $NR^{13}R^{14}$, OR^{13}, halogen, C_1 to C_{10} alkyl, C_3 to C_{10} cyclokalkyl, C_3 to C_{10}

cycloalkylmethyl, C_3 to C_{10} alkene, C_3 to C_{10} alkyne, aryl, C_5 to C_{20} alkaryl, fused C_5 to C_{20} aryl or alkaryl and a hydrocarbon chain containing a heterocyclic or fused ring, any of which may be optionally substituted;

providing that when $X^1(YZ)$ is C=O, X^2 is NH and T is a double bond then A has the general formula:



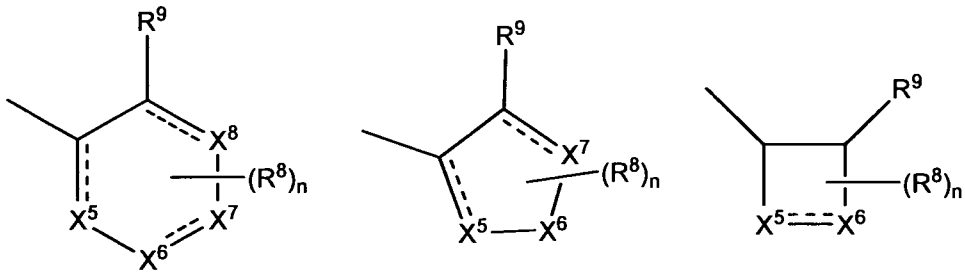
wherein X^5, X^6, $X^7$and X^8 may be independently C, S, O or N;

R^{18} is absent, H or $COOR^{13}$ and R^9 can be H when R^{18} is $COOR^{13}$, more preferably COOH;

but A cannot be phenyl and R^1 to R^5 cannot be $-CF_3$;

and further providing that when $X^1(YZ)$ is C=O, X^2 is NH and T is a cyclopropane ring as defined above then R^9 cannot be tetrazol-5-yl; and

and even further providing that when $X^1(YZ)$ is SO_2, then A has the general formula:

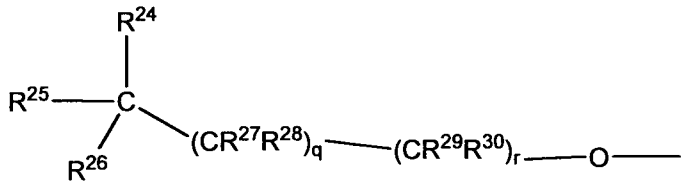


wherein X^5, X^6, X^7 and X^8 may be independently C, S, O or N and R^9 can be H when R^2 and R^3 are each independently a C_1-C_{12} alkyloxy group containing at least one halogen atom, and more preferably when R^2 and R^3 are each $-OCHF_2$.

In some embodiments at least one of R^1, R^2, R^3, R^4, and R^5 is selected from the group consisting of C_1-C_{12} alkyloxy containing at least one halogen atom, C_1-C_{12} alkenyloxy containing at least one halogen atom, and C_1-C_{12} alkynyloxy containing at least one halogen atom.

In another embodiment at least one of R^2 and R^3 is selected from the group consisting of a C_1-C_{12} alkyloxy group containing at least one halogen atom, a C_2-C_{12} alkenyloxy containing at least one halogen atom, a C_2-C_{12} alkynyloxy containing at least one halogen atom and a C_3-C_{12} cycloalkyloxy containing at least one halogen atom and the other R^2 or R^3 is selected from the group consisting of an optionally substituted C_1-C_{12} alkyloxy group, an optionally substituted C_2-C_{12} alkenyloxy, an optionally substituted C_2-C_{12} alkynyloxy and an optionally substituted C_3-C_{12} cycloalkyloxy.

In some embodiments, the C_1-C_{12} alkyloxy group is of Formula (A):



Formula (A)

- wherein: R^{24}, R^{25}, and R^{26} are each independently selected from the group consisting of: H, halogen, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, and optionally substituted C_2-C_{12} alkenyl;
- R^{27}, R^{28}, R^{29}, and R^{30} are each independently selected from the group consisting of: H, halogen, OH, NO_2, CN, and NH_2;
- at least one of R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, and R^{30} is or contains a halogen atom;
- q is an integer selected from the group consisting of: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and
- r is an integer selected from the group consisting of: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

In some embodiments q and r are 0, and at least two of R^{24}, R^{25}, and R^{26} are a halogen.

The halogen may be selected from the group consisting of: fluorine, chlorine, bromine, and iodine. Preferably, the halogen is fluorine. In some embodiments at least one of R^1, R^2, R^3, R^4, and R^5 is selected from the group consisting of–O-CHF_2, -OCF_3, -OCF_2CHF_2. In some embodiments R^3 is the group –O-CHF_2. In some embodiments R^2 and R^3 are the group –O-CHF_2.

In some aspects, R^1 and R^5 are H and R^2 and R^3 are O- R^{16} and O-R^{17}, wherein R^{16} and R^{17} are independently and preferably selected from the group consisting of unsubstituted C_1-C_6 alkyl, preferably methyl or ethyl; C_1-C_6 fluoro substituted alkyl, preferably, F_3CO, F_2HCO, F_2HCF_2CO; or are fused to form a 5 or 6 membered ring, preferably R^2 and R^3 form a bridging difluoromethylenedioxy group or a bridging tetrafluoroethylenedioxy group.

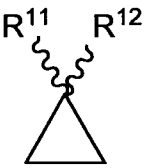
In some embodiments T is a double bond while in other embodiments T is a triple bond.

In some embodiments R^9 is selected from the group consisting of: $COOR^{11}$ and $CONR^{11}R^{12}$. In some embodiments R^9 is selected from the group consisting of: COOH, $CONH_2$, and $CONHCH_3$.

In some embodiments R^9 is $NR^{11}R^{12}$ while in some embodiments R^9 is NH_2.

In some embodiments n is 1.

In some embodiments R^8 is halogen.

In one form of the invention, T is a single bond and one pair of R^6 and R^7 are fused to form a cyclopropane ring of the formula 

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In some embodiments R^2 and R^3 form a bridging difluoromethylenedioxy group or a bridging tetrafluoroethylenedioxy group.

In some embodiments R^6 is CH_3. In some embodiments R^7 is CH_3 or CN. In some embodiments R^8 is H or Me.

In preferred embodiments m is 1 and R^9 is selected from COR^{13} and $CONR^{13}R^{14}$.

In other preferred embodiments R^9 is selected from the group consisting of COOH, $CONH_2$, CONHOH and $CONHCH_3$.

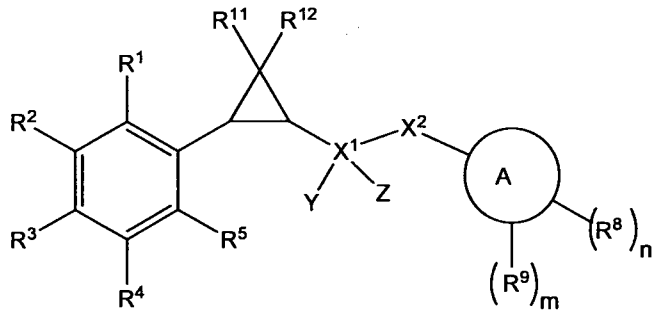
In certain embodiments R^9 is the group tetrazol-5-yl.

In some embodiments R^9 is selected from the group consisting of SO_2R^{13}, $SO_2NR^{13}R^{14}$.

In some more particular embodiments R^9 is selected from the group consisting of SO_2Me, SO_2NH_2, SO_2NHMe, SO_2NMe_2.

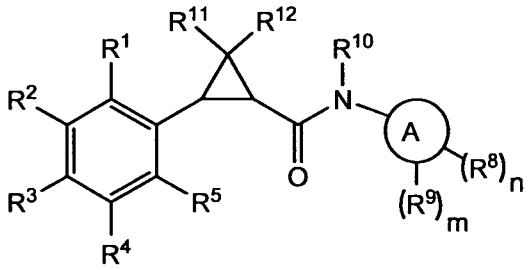
In some embodiments R^9 is $NR^{13}R^{14}$ and in more particular embodiments R^9 is NH_2. In some embodiments R^8 is a halogen. In some embodiments X^2 is NH.

According to a further form of the invention, there is provided a compound of the formula (II)



(II)

Preferred compounds of the invention have the formula (IIa)

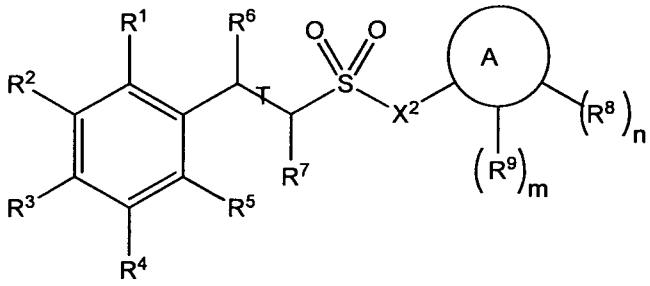


(IIa)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

A, R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11} and R^{12} are as defined above in relation to compounds of formula (I).

A further aspect of the present invention is represented by a compound of the Formula (III)

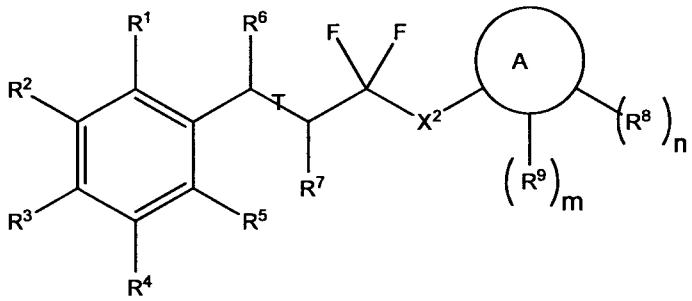


(III)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

A, T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and X^2 are as defined above in relation to compounds of formula (I).

Yet another aspect of the present invention is represented by a compound of the Formula (IV)

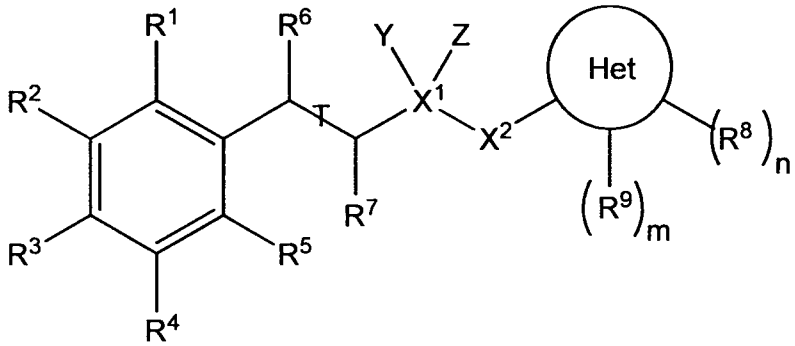


(IV)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

A, T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and X^2 are as defined above in relation to compounds of formula (I).

A further aspect of the present invention may be represented by a compound of Formula (V)

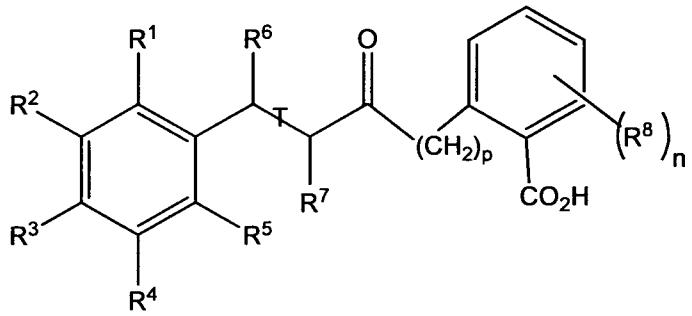


(V)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

Het represents a heterocyclic ring and T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $X^1(YZ)$ and X^2 are as defined above in relation to compounds of formula (I).

According to a further aspect of the present invention, there is provided a compound of formula (VI)



(VI)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and p are as defined above in relation to compounds of formula (I).

In preferred embodiments, R^6 and R^7 are H in the compounds of formulas (III), (IV), (V) and (VI).

In some embodiments T is preferably a double bond in the compounds of formulas (III), (IV), (V) and (VI).

In the compounds of formula (V), certain preferred embodiments have $X^1(YZ)$ as being C=O. In other embodiments X^2 is NH or NR^{13} wherein R^{13} is preferably C_1 to C_6 alkyl, most preferably a methyl group. In preferred embodiments of formula (V), $X^1(YZ)$ is C=O and X^2 is NH.

In preferred embodiments of the compounds of formulae (II) and (IIa), R^{11} and R^{12} are selected from the group consisting of H, CN or halogen. Preferably, R^{11} and R^{12} are H. When R^{11} and/or R^{12} are halogen, the halogen is preferably fluorine.

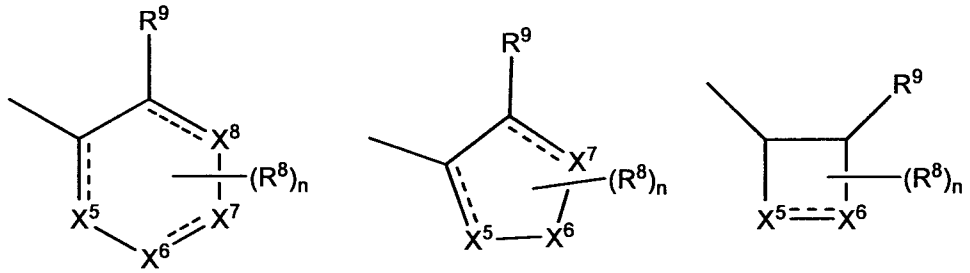
When R^9 is present in the compounds of formulae (II), (IIa), (III), (IV), (V) and (VI), R^9 is preferably selected from the group consisting of CO_2H, CO_2R^{13}, SO_2R^{13}, SO_2NH_2, $SONHR^{13}$, $SONR^{13}_2$, $CONH_2$, $CONHR^{13}$, $CONHOR^{13}$ and 5-tetrazolyl, wherein R^{13} is preferably C_1 to C_6 alkyl, most preferably a methyl group. Alternatively, R^9 is selected

from the group consisting of CO_2H, CO_2R^{13}, SO_2R^{13}, SO_2NH_2, $SONHR^{13}$, $SONR^{13}_2$ and 5-tetrazolyl.

In preferred embodiments of the formulae (II), (IIa), (III), (IV), (V) and (VI), R^1 and R^5 are H and R^2 and R^3 are O-R^{16} and O-R^{17}, wherein R^{16} and R^{17} are independently and preferably selected from the group consisting of unsubstituted C_1-C_6 alkyl, preferably methyl or ethyl; C_1-C_6 fluoro substituted alkyl, preferably, F_3CO, F_2HCO, F_2HCF_2CO; or are fused to form a 5 or 6 membered ring, preferably a fluoro substituted 1,4 dioxane or a fluoro substituted 1,3-dioxolane; or a C_1 to C_6 alkenyl, preferably $-CH_2CCH$.

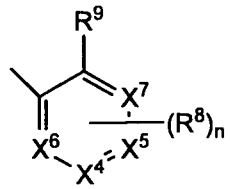
In preferred embodiments of the formulae (II), (IIa), (III), (IV), (V) and (VI), R^{10} is H or a C_1 to C_6 alkyl, preferably, methyl.

In preferred embodiments of the formulae (II), (IIa), (III) and (IV), A has the general formula selected from the group consisting of



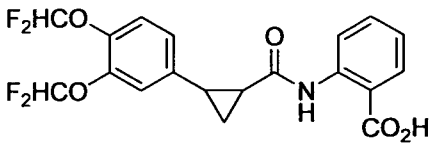
wherein X^5, X^6, X^7 and X^8 may be independently C, S, O or N.

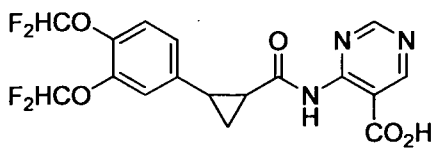
In a particularly preferred embodiments, A has the general formula

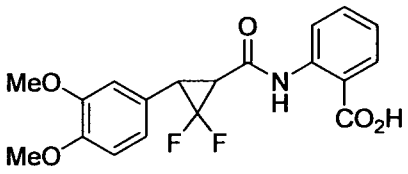


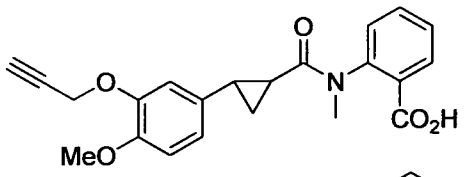
wherein X^4, X^5, X^6 and X^7 may be C or N. More preferably, not more than two of X^4, X^5, X^6 and X^7 may be N.

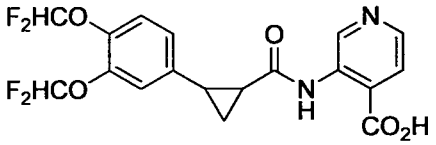
Non-limiting examples of suitable compounds of formula (IIa) include

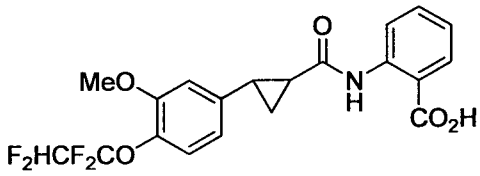


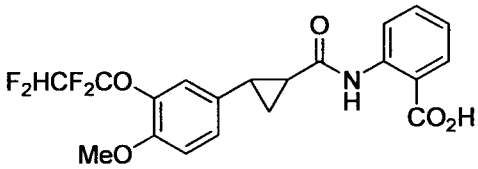


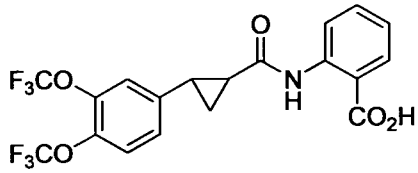


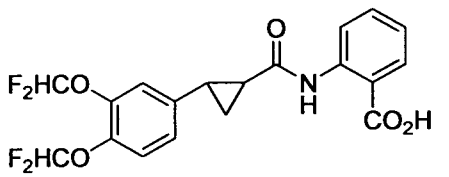


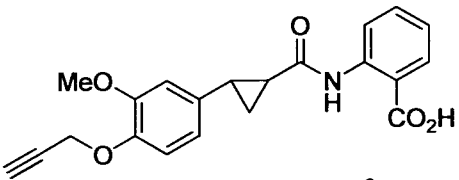


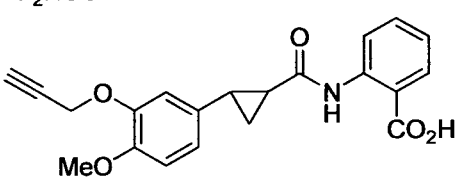


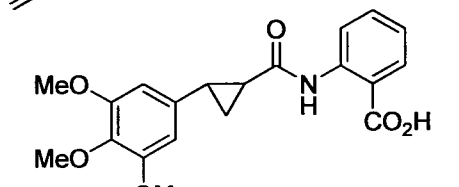


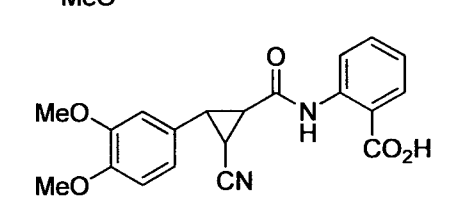


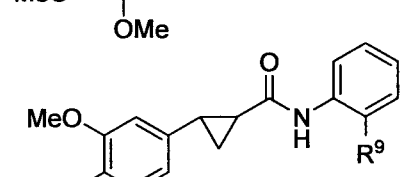






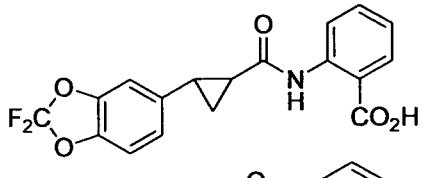


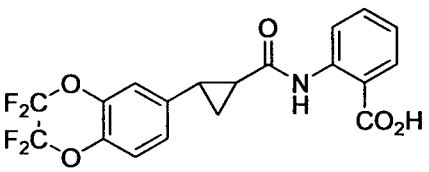


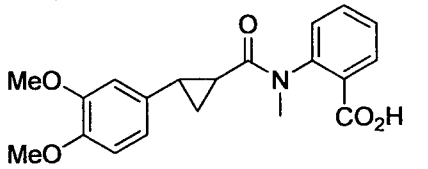


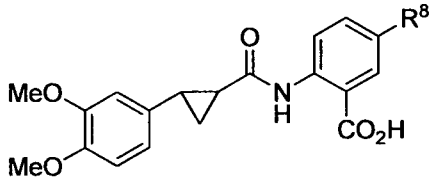
$R^9 = NH_2, CONH_2, CONHMe, CONHOH$

$R^9 = SO_2Me, SO_2NH_2$



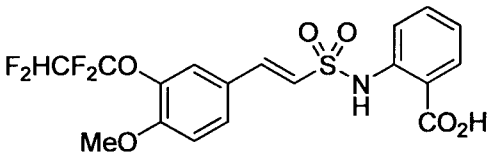


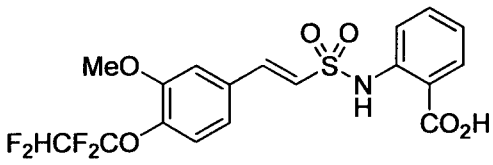


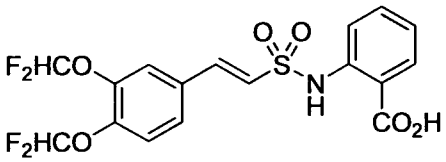


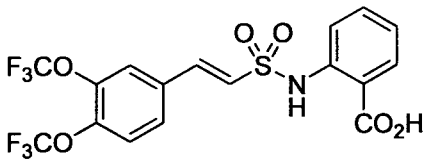
R^8 = Hydrogen, Halogen

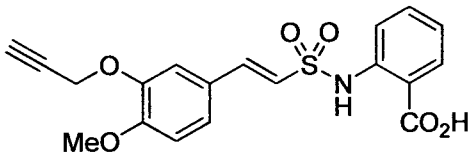
Particular examples of compounds of formula (III) are as follows

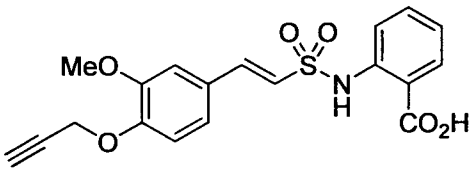


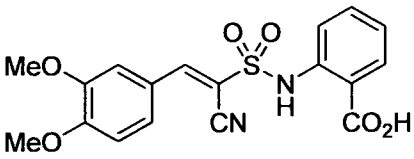


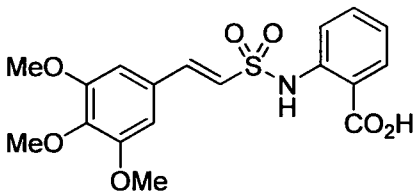


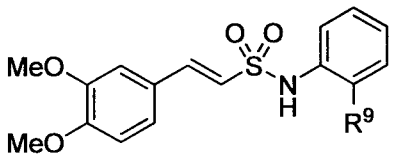


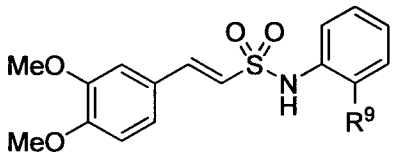






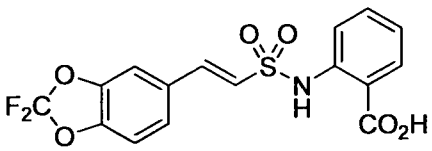


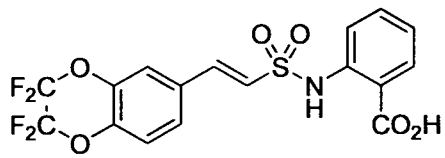


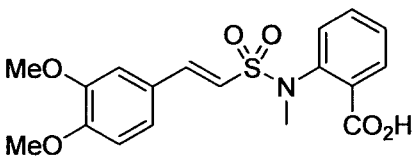


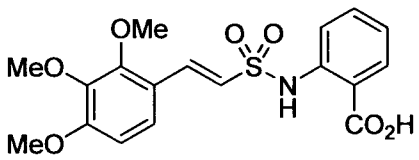
R^9 = SO_2Me, SO_2NH_2, 5-tetrazolyl

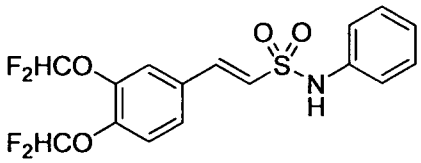
R^9 = NH_2, $CONH_2$, CONHMe, CONHOH

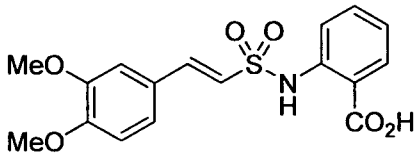




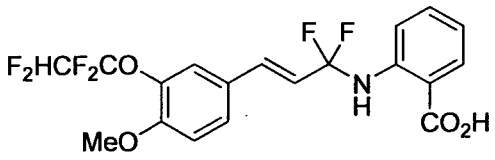


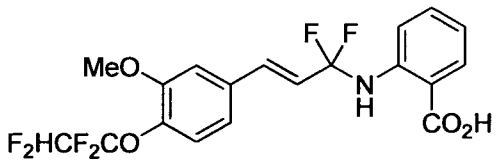


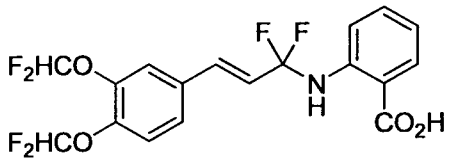


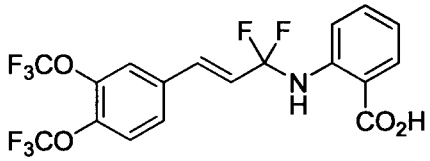


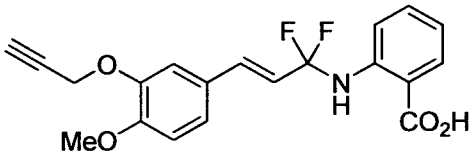
Particular examples of compounds of formula (IV) are as follows

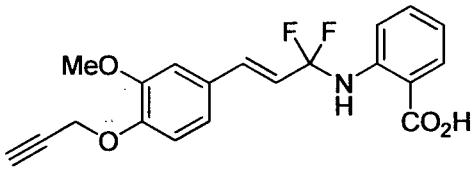


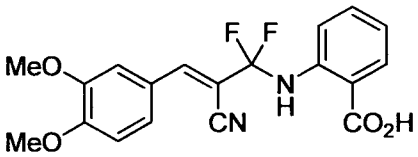


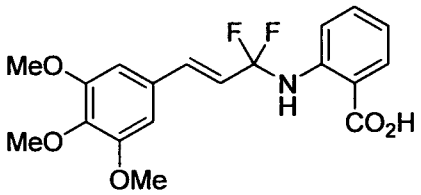


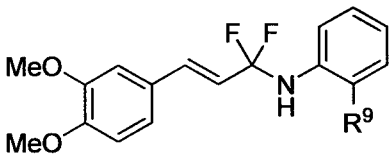




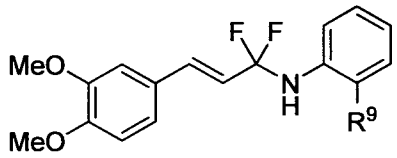




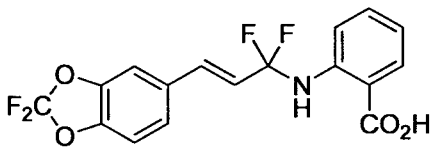


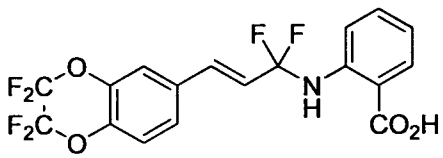


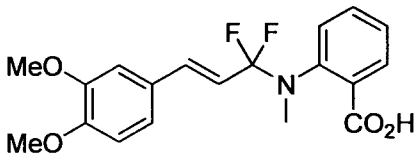
R^9 = SO_2Me, SO_2NH_2, 5-tetrazolyl

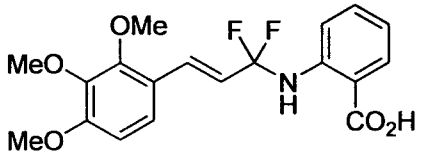


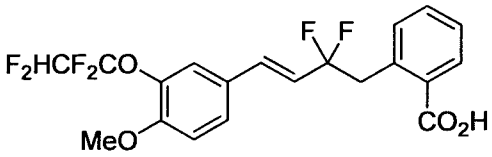
R^9 = NH_2, $CONH_2$, CONHMe, CONHOH

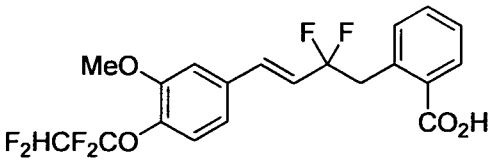


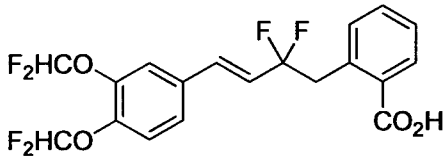


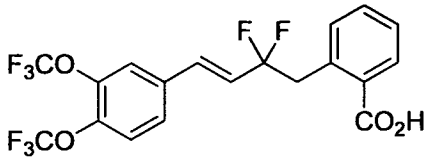


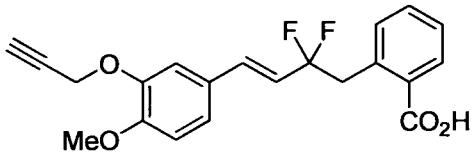


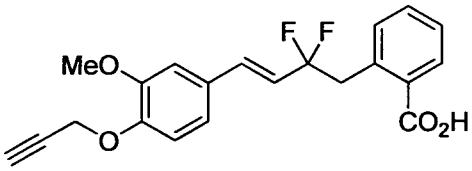


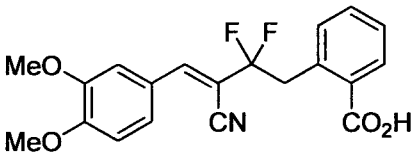


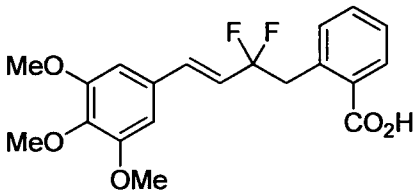


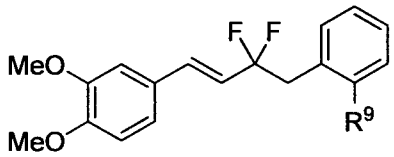


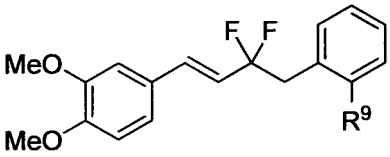






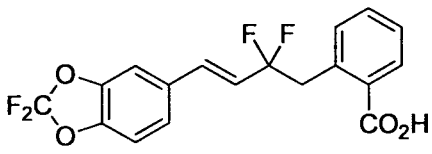


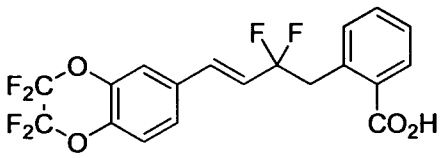


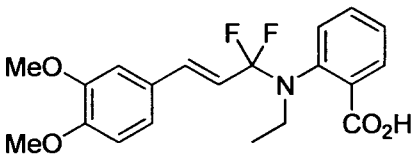


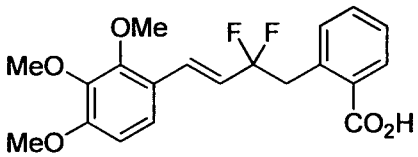
R^9 = SO_2Me, SO_2NH_2, 5-tetrazolyl

R^9 = NH_2, $CONH_2$, CONHMe, CONHOH

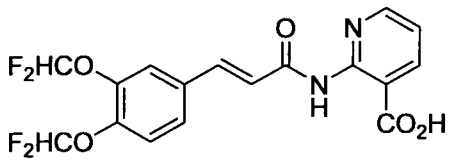


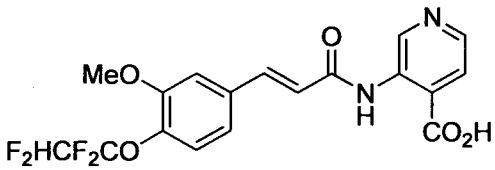


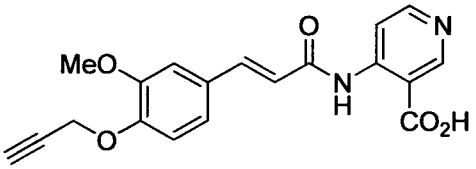


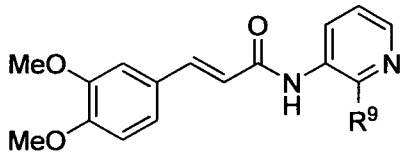


Specific compounds of formula (V) include

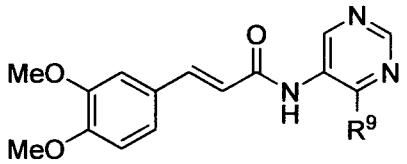


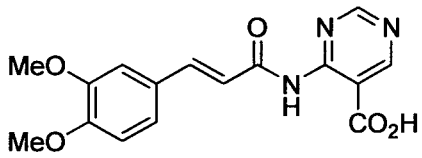




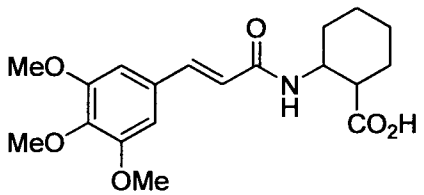


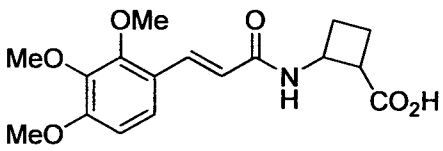
$R^9 = NH_2$, $CONH_2$, CONHMe, CONHOH

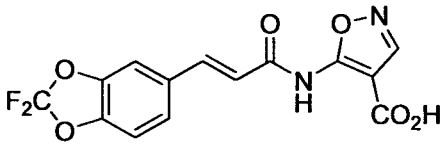


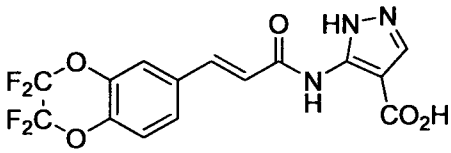


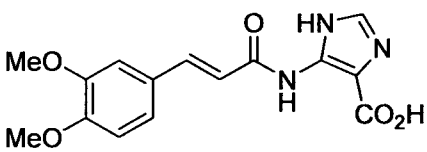
$R^9 = SO_2Me$, SO_2NH_2, SONHMe, $SONMe_2$

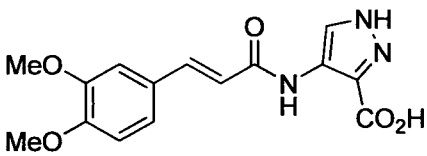


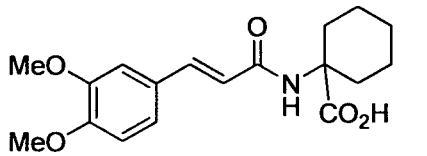


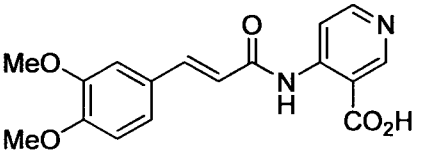


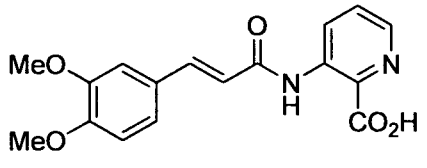




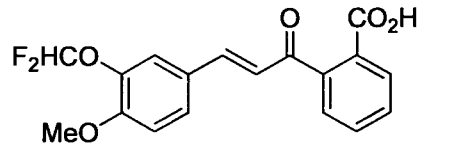


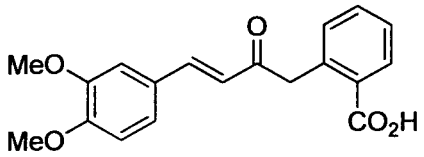


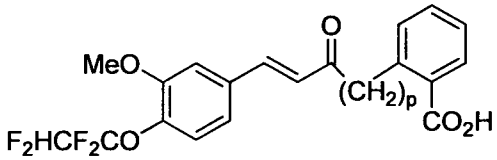


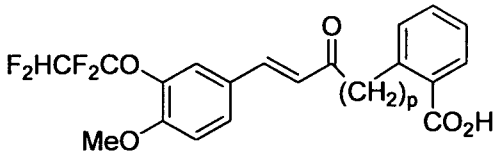


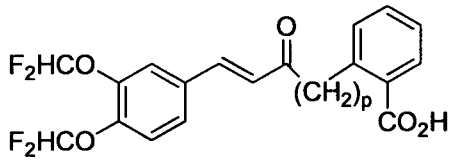
Some specific examples of compounds of formula VI are as follows:

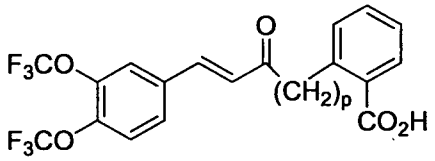


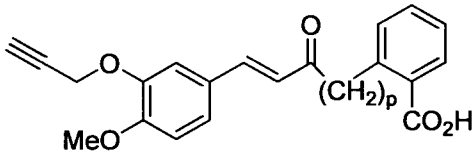


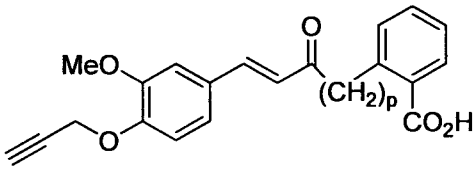


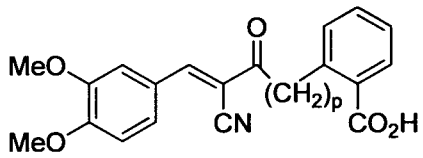


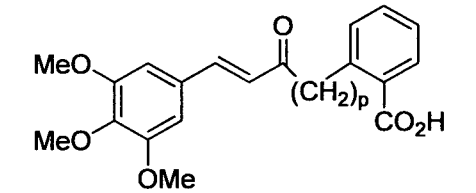


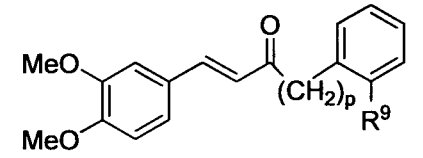


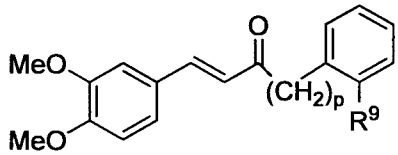






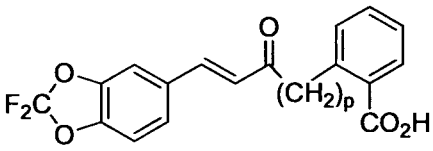


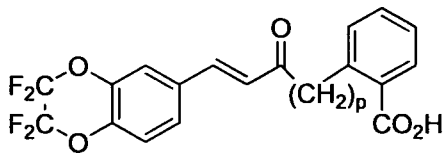




R^9 = SO_2Me, SO_2NH_2, 5-tetrazolyl

R^9 = NH_2, $CONH_2$, CONHMe, CONHOH



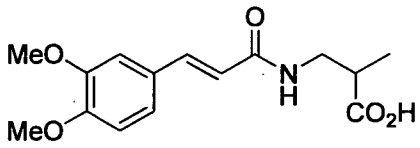


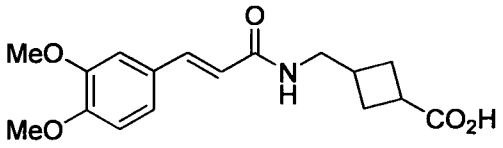
10.

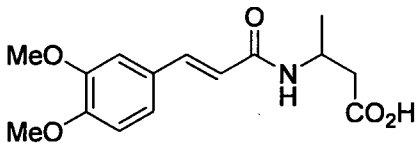
wherein p is 0 or 1.

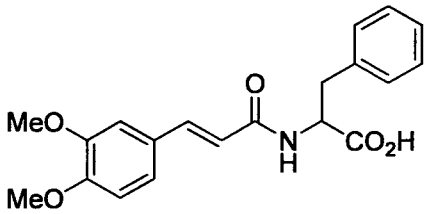
5

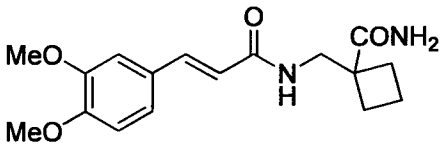
Further derivatives include

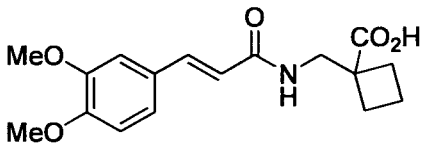












In addition to compounds of formulae (I), (II), (IIa), (III), (IV), (V) and (VI), the embodiments disclosed are also directed to pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites.

The compounds of the present invention may have anti-fibrotic, anti-inflammatory, anti-proliferative or anti-neoplastic activity and may, therefore, find use as an alternative and/or adjunct to Tranilast.

Detailed Description

In this specification a number of terms are used which are well known to a skilled addressee. Nevertheless for the purposes of clarity a number of terms will be defined.

As used herein, the term unsubstituted means that there is no substituent or that the only substituents are hydrogen.

The term "optionally substituted" as used throughout the specification denotes that the group may or may not be further substituted or fused (so as to form a polycyclic system), with one or more non-hydrogen substituent groups. In certain embodiments the substituent groups are one or more groups independently selected from the group

consisting of halogen, =O, =S, -CN, -NO_2, -CF_3, -OCF_3, -$OCHF_2$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxycycloalkyl, alkoxyheterocycloalkyl, alkoxyaryl, alkoxyheteroaryl, alkoxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, -COOH, -COR^{11}, -$C(O)OR^{11}$, $CONHR^{11}$, $NHCOR^{11}$, $NHCOOR^{11}$, $NHCONHR^{11}$, $C(=NOH)R^{11}$, -SH, -SR^{11}, -OR^{11}, and acyl, wherein R^{11} is H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} heterocycloalkyl, optionally substituted C_1-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, optionally substituted C_1-C_{18} heteroaryl, and acyl.

"Alkyl" as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, such as a C_1-C_{14} alkyl, a C_1-C_{10} alkyl or a C_1-C_6 unless otherwise noted. Examples of suitable straight and branched C_1-C_6 alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, hexyl, and the like. The group may be a terminal group or a bridging group.

"Alkylamino" includes both mono-alkylamino and dialkylamino, unless specified. "Mono-alkylamino" means a –NH-Alkyl group, in which alkyl is as defined above. "Dialkylamino" means a –N(alkyl)$_2$ group, in which each alkyl may be the same or different and are each as defined herein for alkyl. The alkyl group may be a C_1-C_6 alkyl group. The group may be a terminal group or a bridging group.

"Arylamino" includes both mono-arylamino and di-arylamino unless specified. Mono-arylamino means a group of formula arylNH-, in which aryl is as defined herein. Di-arylamino means a group of formula (aryl)$_2$N- where each aryl may be the same or

different and are each as defined herein for aryl. The group may be a terminal group or a bridging group.

"Acyl" means an alkyl-CO- group in which the alkyl group is as described herein. Examples of acyl include acetyl and benzoyl. The alkyl group may be a C_1-C_6 alkyl group. The group may be a terminal group or a bridging group.

"Alkenyl" as a group or part of a group denotes an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched such as a group having 2-14 carbon atoms, 2-12 carbon atoms, or 2-6 carbon atoms, in the normal chain. The group may contain a plurality of double bonds in the normal chain and the orientation about each is independently E or Z. Exemplary alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and nonenyl. The group may be a terminal group or a bridging group.

"Alkoxy" refers to an -O-alkyl group in which alkyl is defined herein. The alkoxy may be a C_1-C_6 alkoxy. Examples include, but are not limited to, methoxy and ethoxy. The group may be a terminal group or a bridging group.

"Alkenyloxy" refers to an -O- alkenyl group in which alkenyl is as defined herein. Preferred alkenyloxy groups are C_2-C_6 alkenyloxy groups. The group may be a terminal group or a bridging group.

"Alkynyloxy" refers to an –O-alkynyl group in which alkynyl is as defined herein. Preferred alkynyloxy groups are C_2-C_6 alkynyloxy groups. The group may be a terminal group or a bridging group.

"Alkoxycarbonyl" refers to an –C(O)-O-alkyl group in which alkyl is as defined herein. The alkyl group may be a C_1-C_6 alkyl group. Examples include, but not limited to, methoxycarbonyl and ethoxycarbonyl. The group may be a terminal group or a bridging group.

"Alkylsulfinyl" means a –S(O)-alkyl group in which alkyl is as defined above. The alkyl group is preferably a C_1-C_6 alkyl group. Exemplary alkylsulfinyl groups include, but not limited to, methylsulfinyl and ethylsulfinyl. The group may be a terminal group or a bridging group.

"Alkylsulfonyl" refers to a $-S(O)_2$-alkyl group in which alkyl is as defined above. The alkyl group may be a C_1-C_6 alkyl group. Examples include, but not limited to methylsulfonyl and ethylsulfonyl. The group may be a terminal group or a bridging group.

"Alkynyl" as a group or part of a group means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched and may have from 2-14 carbon atoms, 2-12 carbon atoms, or 2-6 carbon atoms in the normal chain. Exemplary structures include, but are not limited to, ethynyl and propynyl. The group may be a terminal group or a bridging group.

"Alkylaminocarbonyl" refers to an alkylamino-carbonyl group in which alkylamino is as defined above. The group may be a terminal group or a bridging group.

"Cycloalkyl" refers to a saturated or partially saturated, monocyclic or fused or spiro polycyclic, carbocycle that may contain from 3 to 9 carbons per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. It includes monocyclic systems such as cyclopropyl and cyclohexyl, bicyclic systems such as decalin, and polycyclic systems such as adamantane. The group may be a terminal group or a bridging group.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and may have from 5-10 carbon atoms per ring. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. The cycloalkenyl group may be substituted by one or more substituent groups. The group may be a terminal group or a bridging group.

The above discussion of alkyl and cycloalkyl substituents also applies to the alkyl portions of other substituents, such as without limitation, alkoxy, alkyl amines, alkyl ketones, arylalkyl, heteroarylalkyl, alkylsulfonyl and alkyl ester substituents and the like.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl. The group may be a terminal group or a bridging group.

"Halogen" represents fluorine, chlorine, bromine or iodine.

"Heterocycloalkyl" refers to a saturated or partially saturated monocyclic, bicyclic, or polycyclic ring containing at least one heteroatom selected from nitrogen, sulfur, oxygen. The heterocycloalkyl group may have from 1 to 3 heteroatoms in at least one ring. Each ring may be from 3 to 10 membered, such as 4 to 7 membered. Examples of suitable heterocycloalkyl substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, and 1,4-oxathiapane. The group may be a terminal group or a bridging group.

"Heterocycloalkenyl" refers to a heterocycloalkyl as described above but containing at least one double bond. The group may be a terminal group or a bridging group.

"Heterocycloalkylalkyl" refers to a heterocycloalkyl-alkyl group in which the heterocycloalkyl and alkyl moieties are as previously described. Exemplary heterocycloalkylalkyl groups include (2-tetrahydrofuryl)methyl, (2-tetrahydrothiofuranyl) methyl. The group may be a terminal group or a bridging group.

"Heteroalkyl" refers to a straight- or branched-chain alkyl group that may have from 2 to 14 carbons, such as 2 to 10 carbons in the chain, one or more of which has been replaced by a heteroatom selected from S, O, P and N. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary alkyl amines, amides, alkyl sulfides, and the like. The group may be a terminal group or a bridging group. As used herein reference to the normal chain when used in the context of a bridging group refers to the direct chain of atoms linking the two terminal positions of the bridging group.

"Aryl" as a group or part of a group denotes (i) an optionally substituted monocyclic, or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) that may have from 5 to 12 atoms per ring. Examples of aryl groups include phenyl, naphthyl, and the like; (ii) an optionally substituted partially saturated bicyclic aromatic carbocyclic moiety in which a phenyl and a C_{5-7} cycloalkyl or C_{5-7} cycloalkenyl group are fused together to form a cyclic structure, such as tetrahydronaphthyl, indenyl or indanyl. The group may be a terminal group or a bridging group.

"Arylalkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Exemplary arylalkenyl groups include phenylallyl. The group may be a terminal group or a bridging group.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C_{1-5} alkyl moiety. Exemplary arylalkyl groups include benzyl, phenethyl and naphthelenemethyl. The group may be a terminal group or a bridging group.

"Heteroaryl" either alone or as part of a group refers to groups containing an aromatic ring (such as a 5 or 6 membered aromatic ring) having one or more heteroatoms as ring atoms in the aromatic ring with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include nitrogen, oxygen and sulphur. Examples of heteroaryl include thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, isoindolizine, xantholene, phenoxatine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, cinnoline, carbazole, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isooxazole, furazane, phenoxazine, 2-, 3- or 4- pyridyl, 2-, 3-, 4-, 5-, or 8- quinolyl, 1-, 3-, 4-, or 5- isoquinolinyl 1-, 2-, or 3- indolyl, and 2-, or 3-thienyl. The group may be a terminal group or a bridging group.

"Heteroarylalkyl" means a heteroaryl-alkyl group in which the heteroaryl and alkyl moieties are as previously described. The heteroarylalkyl groups may contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl. The group may be a terminal group or a bridging group.

"Lower alkyl" as a group means, unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having 1 to 6 carbon atoms in the chain, for example 1 to 4 carbons such as methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl). The group may be a terminal group or a bridging group.

As would be understood by the skilled person, throughout the synthesis of the compounds of Formula (I) it may be necessary to employ a protecting group on the amino group and/or on the carboxyl group in order to reversibly preserve a reactive

amino or carboxyl functionality while reacting other functional groups on the compound. In such a case, the free amino group and/or the free carboxyl groups of the compounds of Formula (I) can be liberated either by deprotection of the amino group followed by deprotection of the acid moieties or *vice versa*.

Examples of suitable amino protecting groups that may be used include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl ('CBz'), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4cyanobenzyloxycarbonyl, t-butoxycarbonyl ('tBoc'), 2-(4-xenyl)-isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxy-carbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfono)-ethoxycarbonyl, 2-(methylsulfono)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxycarbonyl ("FMOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decycloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonlyl and the like; benzoylmethylsulfono group, 2-nitrophenylsulfenyl, diphenylphosphine oxide, and the like. The actual amino protecting group employed is not critical so long as the derivatised amino group is stable to the condition of subsequent reaction(s) and can be selectively removed as required without substantially disrupting the remainder of the molecule including any other amino protecting group(s). Preferred amino-protecting groups are t-butoxycarbonyl (Boc), and benzyloxycarbonyl (Cbz). Further examples of these groups are found in: Greene, T. W. and Wuts, P. G. M., Protective Groups in Organic Synthesis, Second edition; Wiley-Interscience: 1991; Chapter 7; McOmie, J. F. W. (ed.), Protective Groups in Organic Chemistry, Plenum Press, 1973; and Kocienski, P. J., Protecting Groups, Second Edition, Theime Medical Pub., 2000.

Examples of carboxyl protecting groups that may be used include methyl, ethyl, n-propyl, i-propyl, p-nitrobenzyl, p-methylbenzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-

methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2'4,4'-tetramethoxybenzhydryl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4,'4"-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, β-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonoethyl, 4-nitrobenzylsulfonoethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl, and the like. Preferred carboxyl protecting groups are methyl and t-butyl. Further examples of these groups are found in: Greene, T. W. and Wuts, P. G. M., Protective Groups in Organic Synthesis, Second edition; Wiley-Interscience: 1991; McOmie, J. F. W. (ed.), Protective Groups in Organic Chemistry, Plenum Press, 1973; and Kocienski, P. J., Protecting Groups, Second Edition, Theime Medical Pub., 2000.

It is understood that included in the family of compounds of Formula (I) are isomeric forms including diastereoisomers, enantiomers, tautomers, and geometrical isomers in "E" or "Z" configurational isomer or a mixture of E and Z isomers. It is also understood that some isomeric forms such as diastereomers, enantiomers, and geometrical isomers can be separated by physical and/or chemical methods and by those skilled in the art.

Some of the compounds of the disclosed embodiments may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof, are intended to be within the scope of the subject matter described and claimed.

In the cyclopropane derivatives of the present invention, it is understood that the general formula and representative compounds refer to both cis and trans isomers as either single isomers or any mixture thereof and all isomers and mixtures thereof are intended to fall within the scope of the subject matter described and claimed. Where R^6 and R^7 are different, it will be understood that either the R or S configurations or any mixture thereof is included within the scope of the subject matter described and claimed.

Additionally, formulae (I), (II), (IIa), (III), (IV), (V) and (VI) are intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, each formula includes compounds having the indicated structure, including the hydrated as well as the non-hydrated forms.

In addition to compounds of the formulae (I), (II), (IIa), (III), (IV), (V) and (VI), the compounds of the various embodiments include pharmaceutically acceptable salts,

prodrugs, N-oxides and active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites.

The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the above-identified compounds, and include pharmaceutically acceptable acid addition salts and base addition salts. Suitable pharmaceutically acceptable acid addition salts of compounds of Formula (I) may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, heterocyclic carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, fumaric, maleic, alkyl sulfonic, arylsulfonic. Suitable pharmaceutically acceptable base addition salts of compounds of Formula (I) include metallic salts made from lithium, sodium, potassium, magnesium, calcium, aluminium, and zinc, and organic salts made from organic bases such as choline, diethanolamine, morpholine. Other examples of organic salts are: ammonium salts, quaternary salts such as tetramethylammonium salt; amino acid addition salts such as salts with glycine and arginine. Additional information on pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Co., Easton, PA 1995. In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

"Prodrug" means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of formula (I). For example an ester prodrug of a compound of formula (I) containing a hydroxyl group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of formula (I) containing a hydroxyl group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gestisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinates. As another example an ester prodrug of a compound of formula (I) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. (Examples of ester prodrugs are those described by F.J. Leinweber, Drug Metab. Res.,18:379, 1987).

The term "pharmaceutically acceptable" refers generally to a substance or composition that is compatible chemically and/or toxicologically with the other ingredients including a formulation, and/or the subject being treated.

The term "compounds of the present invention" (unless specifically identified otherwise) refers generally to compounds, prodrugs thereof, pharmaceutically acceptable salts of the compounds and/or prodrugs, and hydrates or solvates of the compounds, salts, and/or prodrugs, as well as all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labelled compounds. The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

The term "derivative thereof" when used in reference to compounds of the present invention refers generally to prodrugs, pharmaceutically acceptable salts of the compounds and/or prodrugs, and hydrates or solvates of the compounds, salts, and/or prodrugs.

The compounds of the present invention may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are commercially available or can be synthesised using known procedures or adaptations thereof. Whilst the preparation of particular compounds is outlined below, the skilled person will also recognize that the chemical reactions described may be readily adapted to prepare a number of other agents of the various embodiments. For example, the synthesis of non-exemplified compounds may be successfully performed by modifications apparent to those skilled in the art, e.g. by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. A list of suitable protecting groups in organic synthesis can be found in T.W. Greene's Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, 1991. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the various embodiments.

Reagents useful for synthesizing compounds may be obtained or prepared according to techniques known in the art.

To produce compounds of the present invention in which T is a single bond the cinnamoyl benzamide (1) can be reduced by hydrogenation with a suitable catalyst, such as palladium on carbon, $RhCl(PPh_3)_3$, or by any other methods known in the art (see J. March, *Advanced Organic Chemistry*, John Wiley & Sons, New York 1985, pp. 694).

The compounds of the invention and intermediates in their synthesis can be isolated from a reaction mixture using standard work-up and purification procedures. Suitable procedures include solvent extraction, chromatography (thin or thick layer chromatography, HPLC, flash chromatography, MPLC, etc.), recrystallisation etc.

The present invention includes salts of the compounds of Formula (I). The salts may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or they may be useful for identification, characterisation or purification. The salts can exist in conjunction with the acidic or basic portion of the molecule and can exist as acid addition, primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, acid addition salts are prepared by the reaction of an acid with a compound of Formula (I). The alkali metal and alkaline earth metal salts are generally prepared by the reaction of the hydroxide form of the desired metal salt with a compound of Formula (I).

Acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric, salicyclic, o-acetoxybenzoic, or organic sulphonic, 2-hydroxyethane sulphonic, toluene-p-sulphonic, or naphthalene-2-sulphonic acid.

The present invention also includes esters of the compounds of Formula (I), such esters being for example aliphatic esters such as alkyl esters. The esters of the compounds of Formula (I) may be pharmaceutically acceptable metabolically labile esters. These are ester derivatives of compounds of Formula (I) that are hydrolysed *in vivo* to afford the compound of Formula (I) and a pharmaceutically acceptable alcohol. Examples of metabolically labile esters include esters formed with alkanols in which the alkanol moiety may be optionally substituted by an alkoxy group, for example methanol, ethanol, propanol and methoxyethanol.

The compounds of the various embodiments may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available. The person skilled in the art will recognise that the chemical reactions described may be readily adapted to prepare a number of other compounds. For example, the synthesis of non-exemplified compounds may be successfully performed by modifications apparent to those skilled in the art, e.g. by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. A list of suitable protecting groups in organic synthesis can be found in T.W. Greene's Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, 1991. Reagents useful for synthesizing compounds may be obtained or prepared according to techniques known in the art.

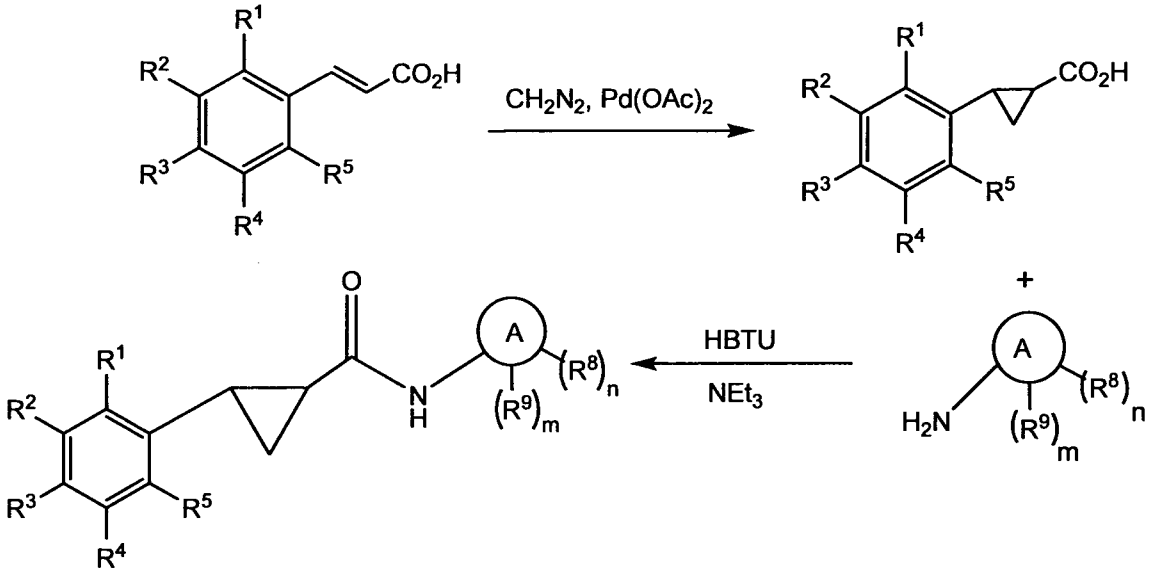
The utility of compounds of Formula (I) can be tested using any of the following methods:

(i) In a renal cell line by measuring proline incorporation after transforming growth factor-β stimulation;

(ii) Matrix synthesis may be stimulated by platelet derived growth factor (PDGF). Accordingly, mesangial cells incubated with PDGF can be used to demonstrate proline incorporation, which is an indicator of matrix synthesis and thereby a model for fibrosis; or

(iii) Matrix synthesis may be stimulated by both angiotensin II or transforming growth factor beta (TGF-β). Accordingly, neonatal cardiac fibroblasts incubated with angiotensin II or TGF-β can be used to demonstrate proline incorporation, which is an indicator of matrix synthesis and thereby a model for fibrosis.

Compounds of formula (II) may suitably be prepared according to scheme I;

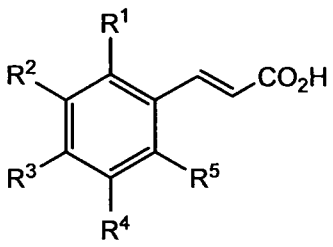


Scheme 1

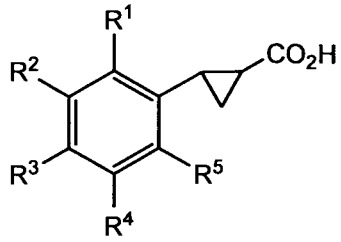
In a preferred form of the preparation according to Scheme 1, the cyclopropanation step is performed with with excess CH_2N_2 and a catalytic quantity of $Pd(OAc)_2$ in a 1:1 mixture of CH_2Cl_2 and diethyl ether. It is also preferred that an esterification step in which the cinnamic acid derivative is reacted with sulphuric acid in methanol to provide the corresponding methyl ester precedes the cyclopropanation step. Preferably, a hydrolysis step in which the cyclopropanated derivative is hydrolysed with aqueous NaOH/MeOH to provide the cyclopropanated carboxylic acid derivative follows the cyclopropanation step.

Thus according to one form of the invention, there is provided a method of preparing a compound of formula II, the method including;

(a) cyclopropanation of a compound of the formula

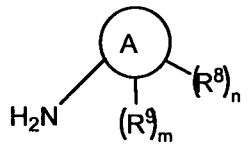


to obtain a compound of the formula

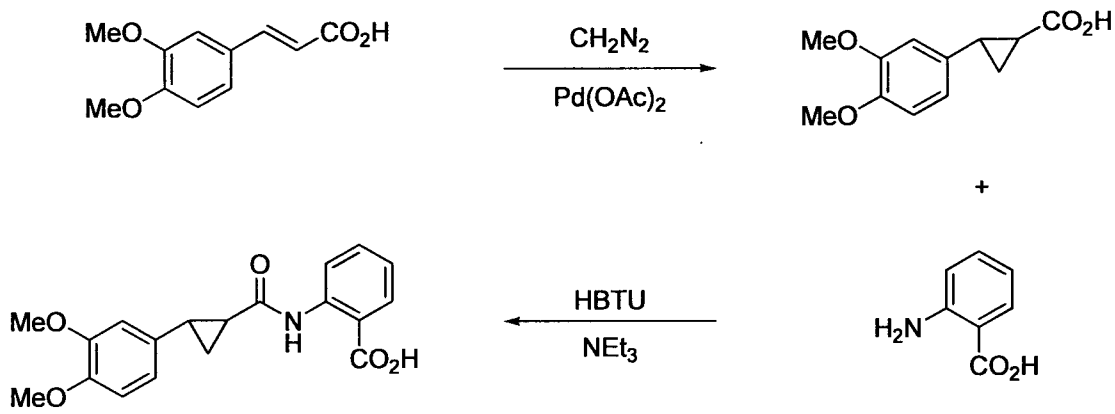


and

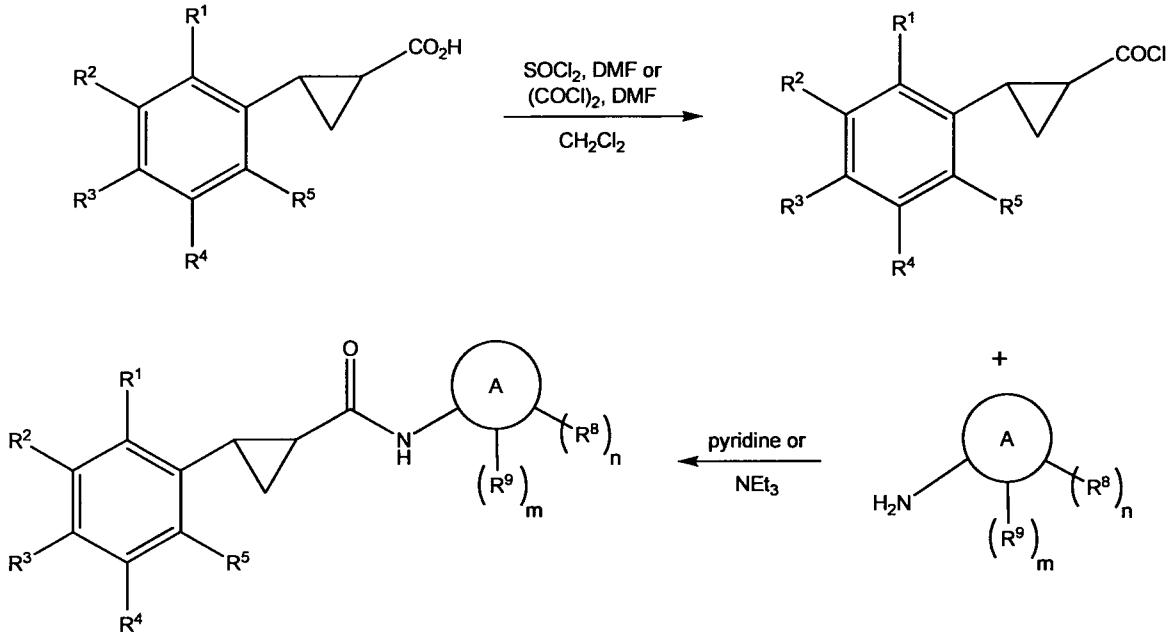
(b) condensing the compound obtained in step (a) with a compound of formula



An exemplary preparation is shown below:



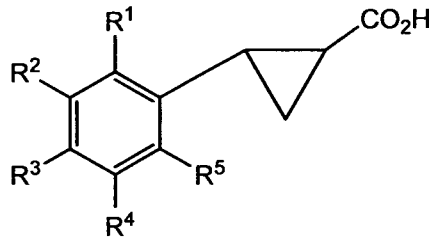
An alternative method for preparing a compound of formula IIa is shown below in Scheme 2.



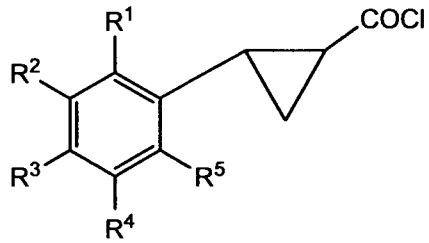
Scheme 2

According to a further aspect of the invention, there is provided a method of preparing a compound of Formula IIa including the steps of:

(a) reacting a compound of the formula

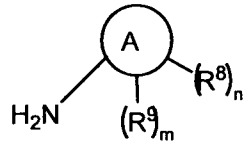


to obtain an acid chloride of the formula

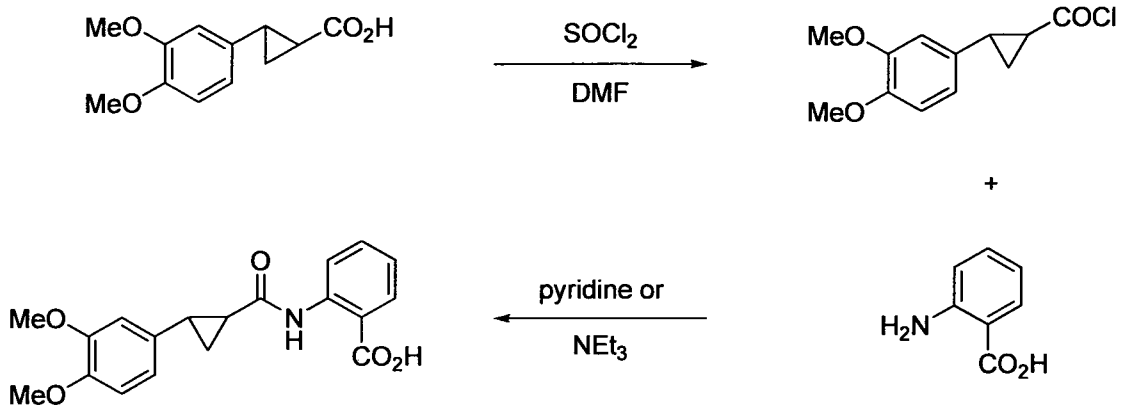


and

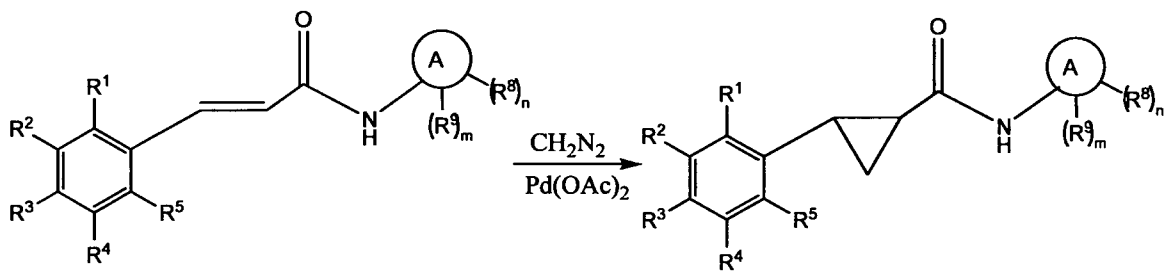
(b) condensing the acid chloride prepared in step (a) with a compound of the formula



An example of preparing a suitable compound of formula IIa is shown below:

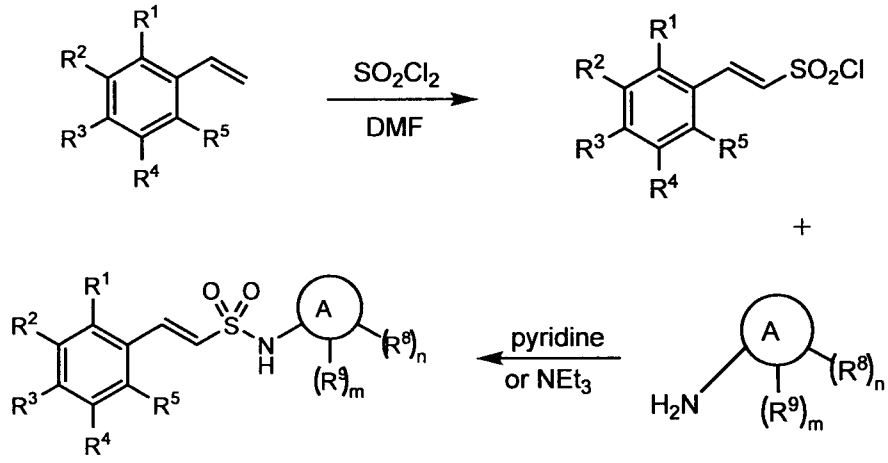


A further method of preparing a compound of formula IIa is shown in scheme 3 below:



Scheme 3

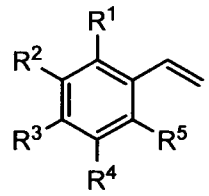
Compounds of formula III may be prepared according to scheme 4 below;



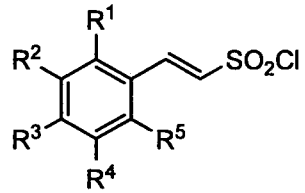
Scheme 4

Thus, according to a further aspect of the invention, there is provided a method for preparing a compound of formula III including the steps of;

(a) reacting a terminal alkene of the formula

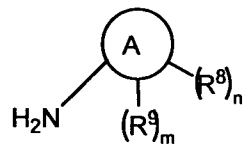


to provide a sulfonyl chloride compound of the formula

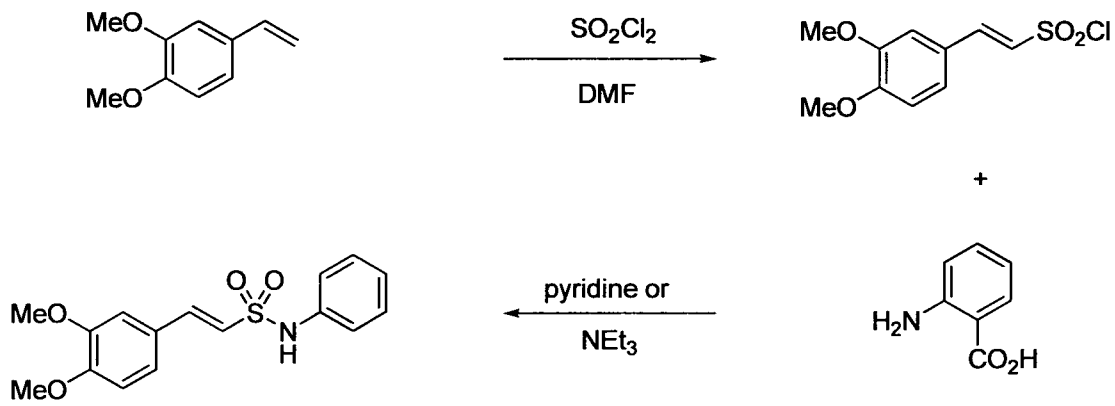


and

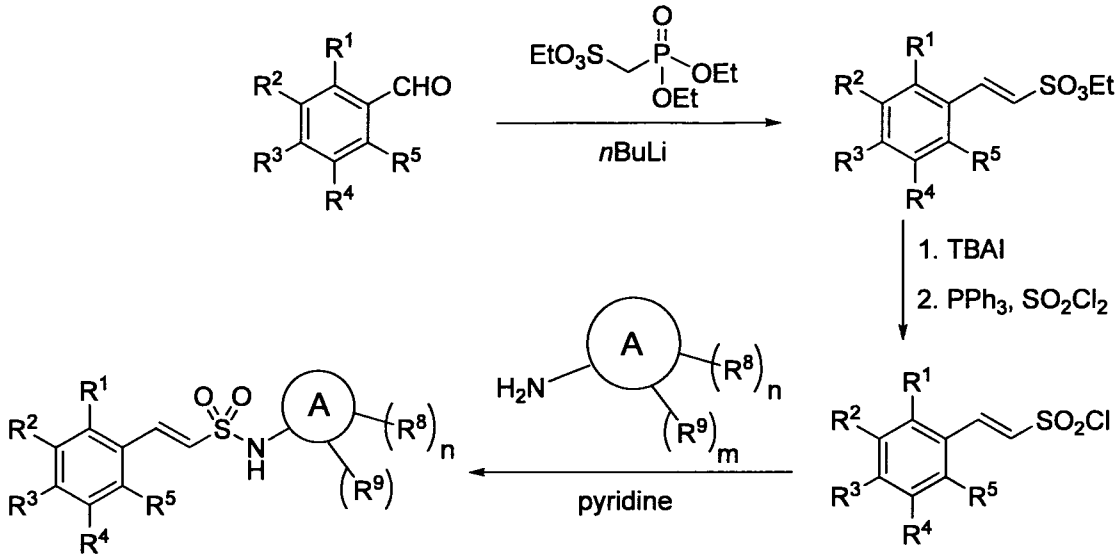
(b) condensing the sulfonyl chloride prepared in step (a) with a compound of formula



An example of preparing a compound of formula III is as follows:



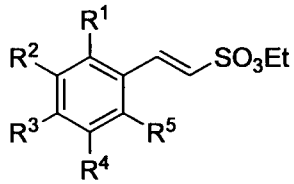
An alternative method for preparing a compound of formula III is shown below in Scheme 5.



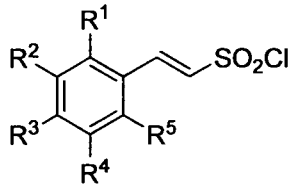
Scheme 5

Thus, according to a further aspect of the invention, there is provided a method of preparing a compound of Formula III including the steps of:

(a) reacting a sulfonate compound of the formula

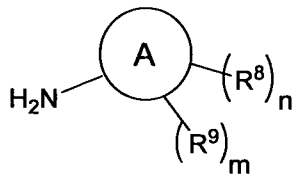


to provide a sulfonyl chloride compound of the formula

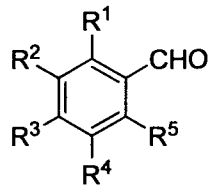


and

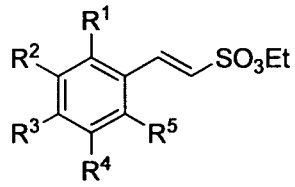
(b) condensing the sulfonyl chloride compound prepared in step (a) with a compound of the formula



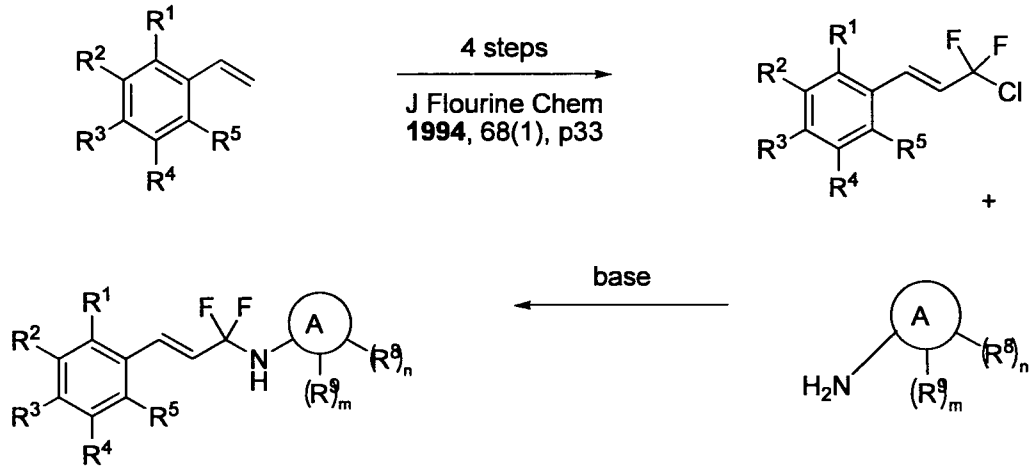
If desired, the method of preparing the compound of Formula III as described immediately above may also include an initial step of reacting an aldehyde compound of the formula



to provide the sulfonate compound of the formula



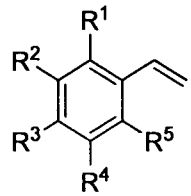
Compounds of Formula IV in which X^2 is NH may be prepared according to scheme 6 below.



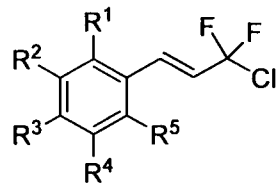
Scheme 6

Thus according to a further aspect of the invention, there is provided a method for preparing a compound of formula IV in which X^2 is NH that includes the steps of;

(a) reacting a terminal alkene of the formula

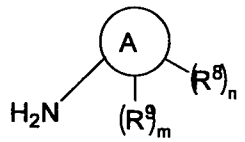


to provide a compound of formula

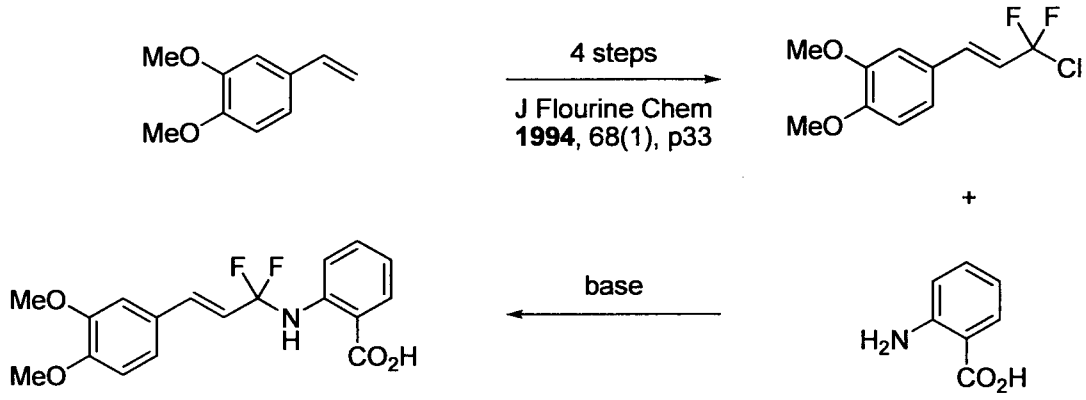


and

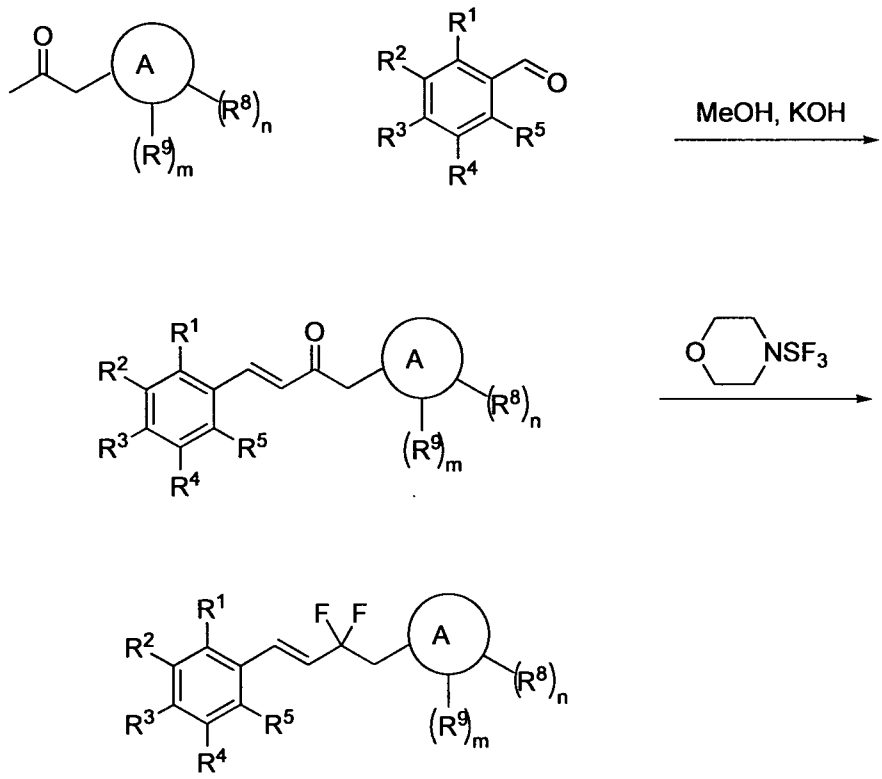
(b) condensing the compound prepared in step (a) with a compound of the formula



A specific example for the preparation of a compound of formula IV is as follows:



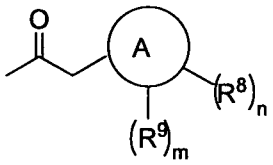
Compounds of formula IV in which X^2 is CH_2 may be prepared by forming the ∝,β-unsaturated ketone and then converting the ketone to the difluorovinyl species using morpholino-SF3 (See *Tetrahedron Letters* (2004), **45**(7), 1527; *Synthesis* (1963), 787) according to scheme 7 below:



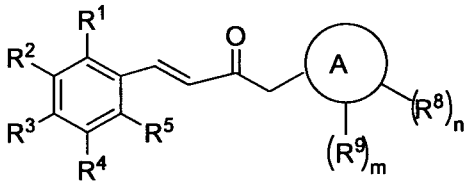
Scheme 7

Thus, according to a further aspect of the invention, there is provided a method for the preparation of compounds of formula IV in which X^2 is CH_2 that includes the steps of;

(a) reacting a compound of the formula

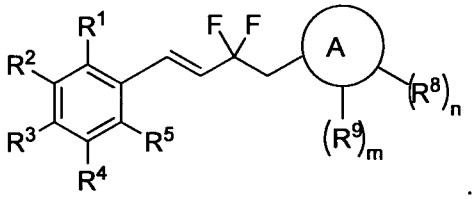


to provide a ketone of the formula

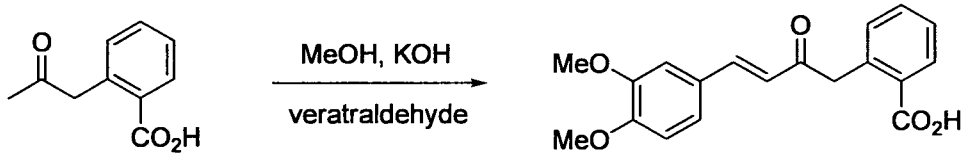


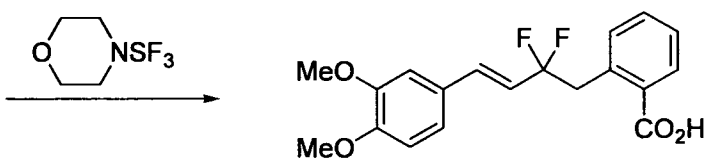
and

(b) converting the ketone prepared in step (a) to a compound of the formula

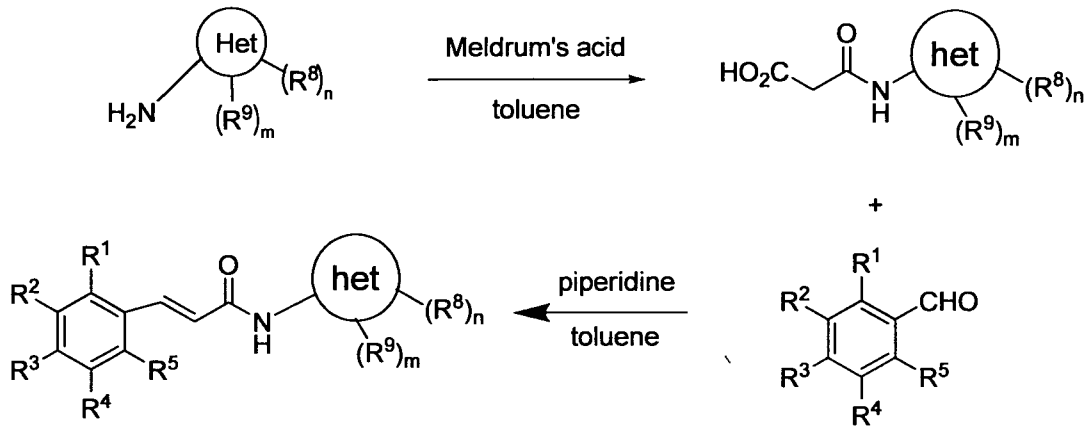


A specific example of such a method is shown below:



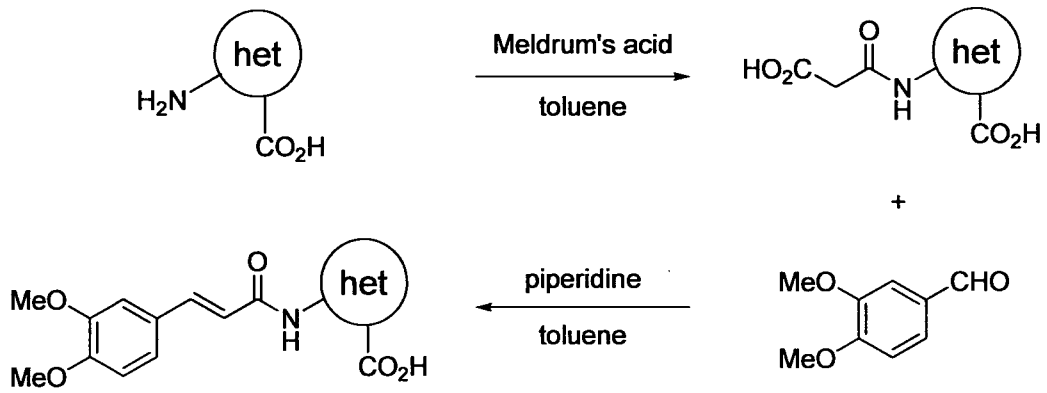


Compounds of formula V in which X^2 is NH may be made by reaction with Meldrum's acid followed by condensation of the malonic-type acid with a suitable aldehyde as shown in the following Scheme 8:

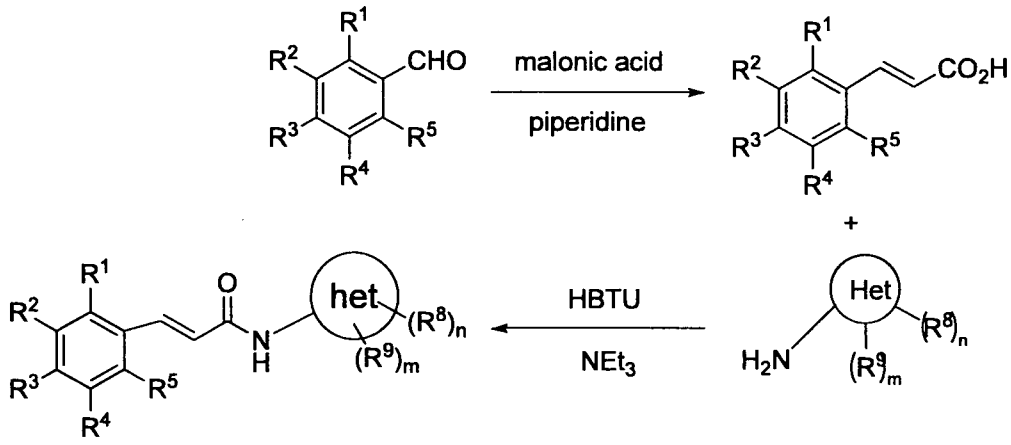


Scheme 8

A specific example of such a preparation is shown below:

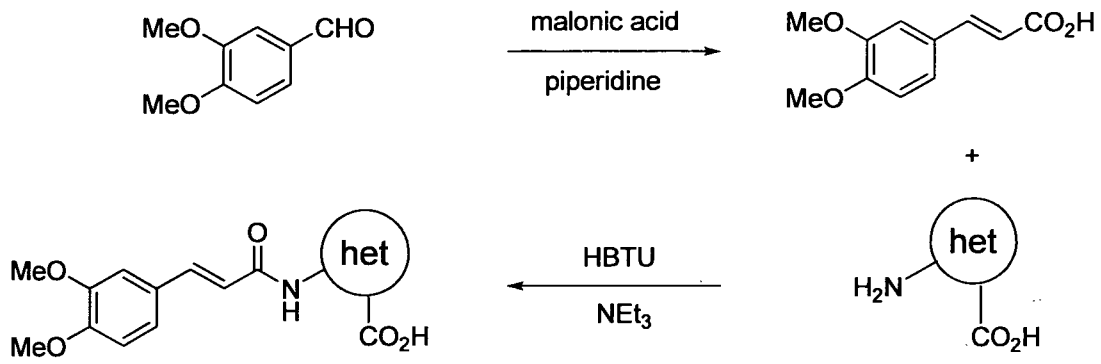


Compounds of formula V may also be prepared by Knoevenagel condensation of a suitable aldehyde with malonic acid then coupling of the cinnamic acid with an aryl amine according to scheme 9 below.

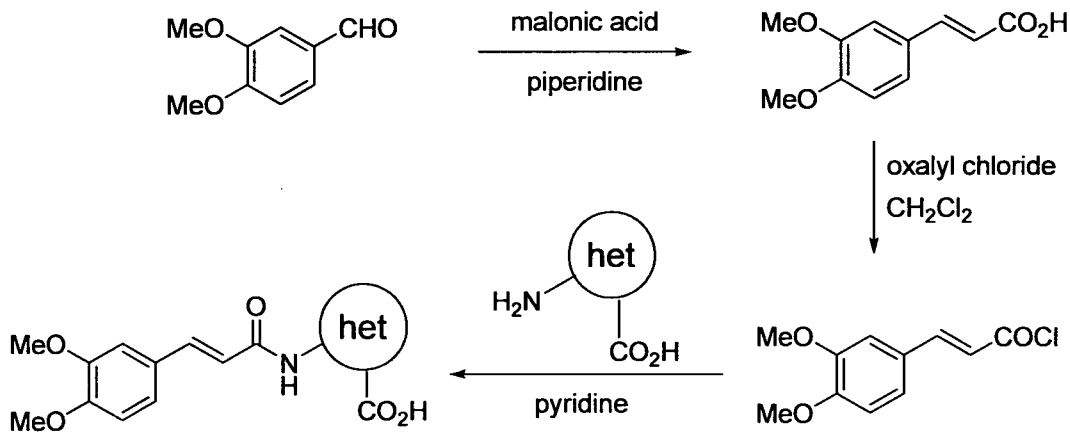


Scheme 9

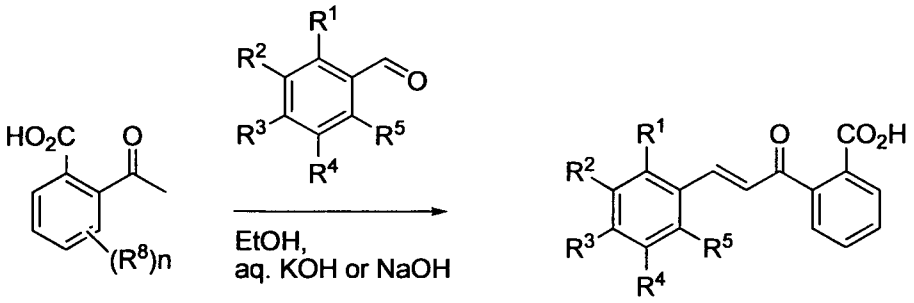
A specific example of such a synthesis is shown below:



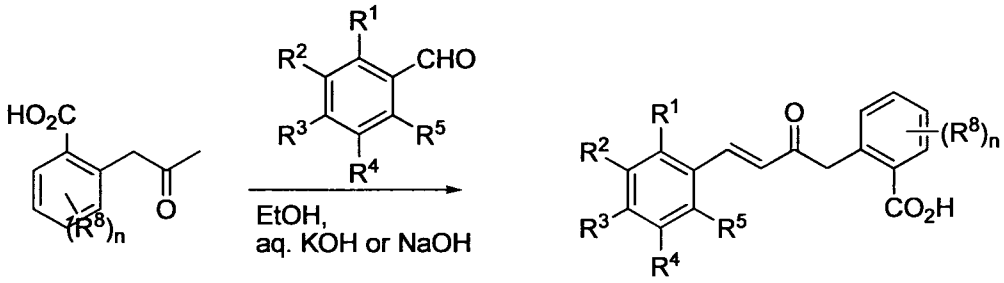
Another specific example of such a synthesis in which the 3,4-dimethoxycinnamic acid is converted to the corresponding acid chloride prior to reaction with a heterocyclic amine is shown below:



Compounds of the formula VI may be prepared by a method as shown in Schemes and 10 and 11 below:



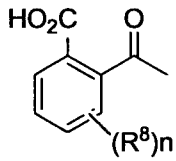
Scheme 10



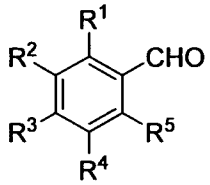
Scheme 11

Thus according to a further broad form of the invention there is provide a method of preparing a compound of formula (VI) including the step of:

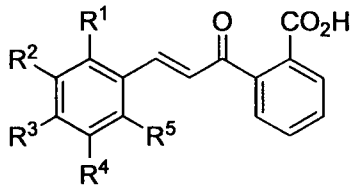
reacting a compound of the formula



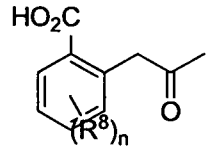
with a compound of the formula



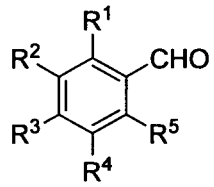
to obtain a compound of the formula



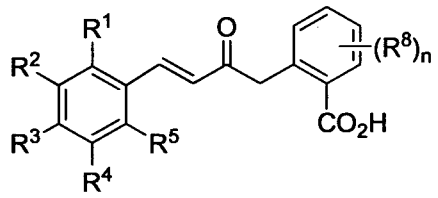
A further form of the invention provides a method of preparing a compound of formula (VI) including the step of reacting a compound of formula



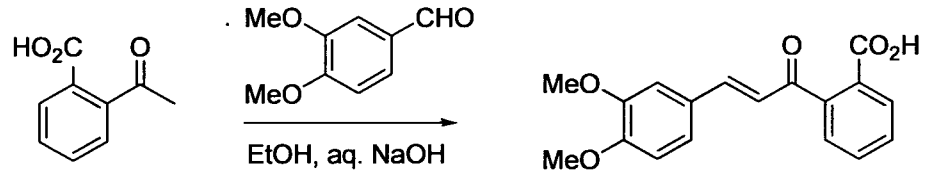
with a compound of formula

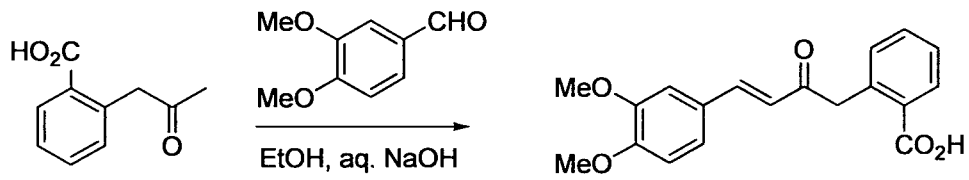


to provide a compound of formula



Specific examples of such a synthesis are shown below:





Examples of materials and methods for use with the compounds of the present invention will now be provided. In providing these examples, it is to be understood that the specific nature of the following description is not to limit the generality of the above description.

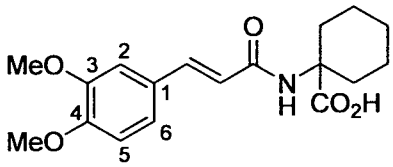
Examples

Experimental

Electrospray ionization (ESI) high resolution mass spectra (HRMS) were obtained on a Finnigan hybrid LTQ-FT mass spectrometer (Thermo Electron Corp.). Proton nuclear magnetic resonance (^{1}H NMR) and proton decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained on Unity 400, Innova 400 or Innova 500 instruments (Melbourne, Australia) operating at 400 or 500 MHz for ^{1}H and at 100 or 125 MHz for ^{13}C. All signals were referenced to solvent peaks ($CDCl_3$: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C; DMSO-d_6: 2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C). Infrared (IR) spectra were obtained using a PerkinElmer Spectrum One FT-IR spectrometer with zinc selenide/diamond Universal ATR Sampling Accessory. Melting points were obtained using a Reichert-Jung hot stage apparatus and are corrected. Analytical thin layer chromatography (TLC) was conducted on 2 mm thick silica gel GF_{254}. Compounds were visualised with solutions of 20% w/w phosphomolybdic acid in ethanol, 20% w/w potassium permanganate in water or under UV (365 nm). Flash chromatography was performed with Merck Silica Gel 60. Petrol refers to the fraction boiling at 40-60 ^{0}C. All other reagents were used as received.

Example 1 - Synthesis of compounds of Formula (I)

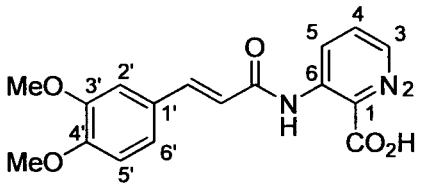
(E)-1-[[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]amino]cyclohexanecarboxylic acid ***(FT101)***



A suspension of (*E*)-3-(3,4-dimethoxyphenyl)-2-propenoic acid (0.25 g, 1.2 mmol) in CH_2Cl_2 (5 mL) was treated with oxalyl chloride (0.41 mL, 4.8 mmol). The solution was stirred at rt for 1 h and the solvent was removed under reduced pressure to give the acid chloride as a yellow solid. 1-Aminocyclohexanecarboxylix acid (0.21 g, 1.4 mmol) was added to a solution of the acid chloride (1.2 mmol) in pyridine (2.0 mL) and the suspension was stirred at rt for 16 h. The solution was diluted with water and the precipitate was collected by filtration. The crude product was recrystallised from EtOAc providing (*E*)-1-[[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]amino]cyclohexanecarboxylic acid (40 mg, 10%) as a colourless crystalline solid; mp 171–173 °C; δ_H (500 MHz, DMSO-d_6) 1.23 (m, 2H, CH_2), 1.45-1.53 (m, 4H, CH_2), 1.67 (m, 2H, CH_2), 2.00 (m, 2H,

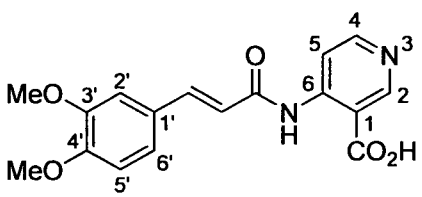
CH_2), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.67 (d, J = 15.5 Hz, 1H, CH=C*H*CO), 6.98 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*5), 7.09 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*6), 7.13 (s, 1H, *H*2), 7.28 (d, J = 15.5 Hz, 1H, C*H*=CHCO), 7.92 (s, 1H, N*H*), 12.05 (s, 1H, CO_2H); δ_C (125 MHz, DMSO-d_6) 21.0, 25.0, 31.8, 55.3, 55.5, 57.8, 109.7, 111.7, 120.0, 121.4, 127.7, 138.6, 148.9, 150.1, 164.8, 175.5; HRMS (ESI) calculated for $C_{18}H_{23}NO_5$ $[M+Na]^+$ 351.1468, found 351.1467; ν_{max} 1137, 1239, 1260, 1516, 1599, 1653, 1731, 2932, 3236, 3334 cm^{-1}.

(E)-[6-[[3-(3,4-Dimethoxyphenyl)-1-oxo-2-propenyl]amino]]-2-pyridinecarboxylic acid ***(FT103)***



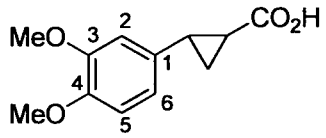
A suspension of (*E*)-3-(3,4-dimethoxyphenyl)-2-propenoic acid (0.25 g, 1.2 mmol) in CH_2Cl_2 (5 mL) was treated with oxalyl chloride (0.41 mL, 4.8 mmol). The solution was stirred at rt for 1 h and the solvent was removed under reduced pressure to give the acid chloride as a yellow solid. 3-Aminopicolinic acid (0.25 g, 1.4 mmol) was added to a solution of the acid chloride (1.2 mmol) in pyridine (2.0 mL) and the suspension was stirred at rt for 4 d. The solution was diluted with water and the precipitate was collected by filtration providing (*E*)-2-(3,4-dimethoxystyryl)-4H-pyrido[2,3-d][1,3]oxazin-4-one (80 mg, 20%) as a brown solid; mp 206–207 °C; δ_H (500 MHz, DMSO-d_6) 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.84 (d, J = 15.5 Hz, 1H, CH=C*H*CO), 6.99 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'), 7.25 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*6'), 7.38 (s, 1H, *H*2'), 7.58 (d, J = 15.5 Hz, 1H, C*H*=CHCO), 7.71 (dd, $J_{3,4}$ = 8.0, $J_{4,5}$ = 5.0 Hz, 1H, *H*4), 7.87 (d, $J_{4,5}$ = 5.0 Hz, 1H, *H*5), 8.47 (d, $J_{3,4}$ = 8.0 Hz, 1H, *H*3), 11.49 (s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 55.5, 55.6, 110.4, 111.6, 119.2, 122.8, 127.1, 127.9, 129.8, 134.0, 137.9, 141.5, 142.3, 149.0, 150.8, 164.8, 166.9; HRMS (ESI) calculated for $C_{17}H_{16}N_2O_5$ $[M+H]^+$ 329.1132, found 329.1131; ν_{max} 808, 1141, 1259, 1508, 1667, 2938 cm^{-1}.

(E)-[6-[[3-(3,4-Dimethoxyphenyl)-1-oxo-2-propenyl]amino]]-3-pyridinecarboxylic acid ***(FT104)***



A suspension of (*E*)-3-(3,4-dimethoxyphenyl)-2-propenoic acid (1.0 g, 4.8 mmol) in CH_2Cl_2 (10 mL) was treated with oxalyl chloride (1.6 mL, 19 mmol). The solution was stirred at rt for 1 h and the solvent was removed under reduced pressure to give the acid chloride as a yellow solid. 4-Aminonicotinic acid (0.73 g, 5.3 mmol) was added to a solution of the acid chloride (4.8 mmol) in pyridine (5.0 mL) and the suspension was heated to reflux and stirred for 5 d. The solution was diluted with water and the precipitate was collected by filtration providing (*E*)-[6-[[3-(3,4-Dimethoxyphenyl)-1-oxo-2-propenyl]amino]]-3-pyridinecarboxylic acid (0.25 g, 16%) as a colourless solid; mp 258–260 °C; δ_H (500 MHz, DMSO-d_6) 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.82 (d, J = 15.5 Hz, 1H, CH=C*H*CO), 7.00 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'), 7.23 (dd, $J_{5',6'}$ = 8.0, $J_{2',6'}$ = 2.0 Hz, 1H, *H*6'), 7.33 (s, $J_{2',6'}$ = 2.0 Hz, 1H, *H*2'), 7.62 (d, J = 15.5 Hz, 1H, C*H*=CHCO), 8.60 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*5), 8.63 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*6), 9.03 (s, 1H, *H*2); HRMS (ESI) calculated for $C_{17}H_{14}N_2O_4$ $[M+H]^+$ 329.1132, found 329.1129; ν_{max} 1140, 1262, 1488, 1623, 2938, 3543 cm^{-1}.

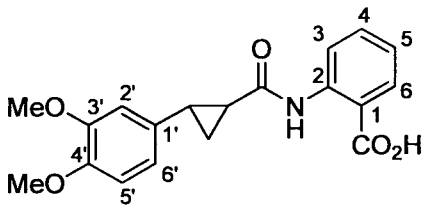
2-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acid



Concentrated sulfuric acid (1.0 mL) was added to a solution of (*E*)-3,4-dimethoxycinnamic acid (2.0 g, 9.6 mmol) in MeOH (50 mL). The solution was heated to reflux for 4 h, cooled to rt and then quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc and the combined organic fractions were washed with water, brine, dried and concentrated providing methyl ester (2.2 g, 95%). A cooled solution of the methyl ester (0.11 g, 0.49 mmol) and $Pd(OAc)_2$ (6 mg, 0.027 mmol) in CH_2Cl_2 (3 mL) and ether (3 mL) was treated with excess CH_2N_2 at 0 °C The suspension was filtered and the filtrate was concentrated. The crude residue was dissolved in MeOH (5 mL) and treated with 1 M NaOH (5 mL). The mixture was stirred at rt for 16 h and then concentrated under reduced pressure to remove the MeOH. The aqueous phase was washed with 50% EtOAc/petrol, acidified with 1 M HCl and then extracted with EtOAc. The combined organic fractions were washed with water, brine, dried and concentrated providing 2-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acid (96 mg, 87%) as a colourless crystalline solid; δ_H (500 MHz, DMSO-d_6) 1.36 (ddd, J = 5.0, J = 4.0, J = 2.0 Hz, 1H, CH), 1.62 (ddd, J = 2.0, J = 4.0, J = 2.0 Hz, 1H, CH), 1.84 (ddd, J = 2.0, J = 4.0, J = 2.0 Hz, 1H, CH), 2.57 (ddd, J = 2.0, J = 4.0, J = 3.0 Hz, 1H, CH), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.65 (d, $J_{5,6}$ = 8.0, 1H, *H*6), 6.66 (s, 1H,

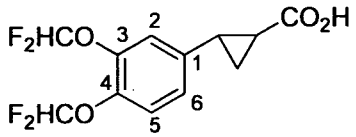
*H*2), 6.78 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*5); δ_C (125 MHz, DMSO-d_6) 7.1, 23.6, 26.9, 55.8, 55.9, 110.1, 111.3, 118.2, 131.9, 147.9, 148.9, 179.8.

2-(2-(3,4-dimethoxyphenyl)cyclopropanecarboxamido)benzoic acid ***(FT111)***



A suspension of 2-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acid (96 mg, 0.41 mmol) in CH_2Cl_2 (1 mL) was treated with oxalyl chloride (0.14 mL, 1.6 mmol). The solution was stirred at rt for 1 h and the solvent was removed under reduced pressure to give the acid chloride. Anthranilic acid (0.11 g, 0.82 mmol) was added to a solution of the acid chloride (0.41 mmol) in pyridine (2.0 mL) and the suspension was stirred at rt for 16 h. The solution was acidified with 1 M HCl and the solvent was decanted and discarded. The crude residue was dissolved in EtOAc and the organic phase was extracted into 1 M $NaHCO_3$ and discarded. The aqueous phase was then acidified with 1 M HCl and extracted with EtOAc. The combined organic fractions were washed with water, brine, dried and concentrated providing 2-(2-(3,4-dimethoxyphenyl)cyclopropanecarboxamido)benzoic acid (65 mg, 46%) as a pale brown solid; mp 159–163 °C; δ_H (500 MHz, DMSO-d_6) 1.39 (m, 1H, CH), 1.48 (m, 1H, CH), 1.94 (m, 1H, CH), 2.40 (m, 1H, CH), 3.72 (s, 3H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 6.72 (d, $J_{5,6}$ = 8.0, 1H, *H*6'), 6.81 (s, 1H, *H*2'), 6.87 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*5'), 7.13 (t, $J_{3,4}$ = $J_{4,5}$ = 7.9 Hz, 1H, *H*4), 7.56 (t, $J_{4,5}$ = $J_{5,6}$ = 7.9 Hz, 1H, *H*5), 7.97 (d, $J_{3,4}$ = 7.9 Hz, 1H, *H*3), 8.46 (d, $J_{5,6}$ = 7.9 Hz, 1H, *H*6), 11.58 (s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 15.9, 25.2, 27.5, 55.5, 55.6, 110.0, 110.3, 112.0, 117.8, 120.0, 122.5, 131.0, 132.8, 133.6, 140.6, 147.4, 148.8, 169.4, 170.1; HRMS (ESI) calculated for $C_{19}H_{19}NO_5$ $[M–H]^-$ 340.1191, found 340.1186; ν_{max} 1023, 1140, 1255, 1516, 1671, 2836, 2921, 3326 cm^{-1}.

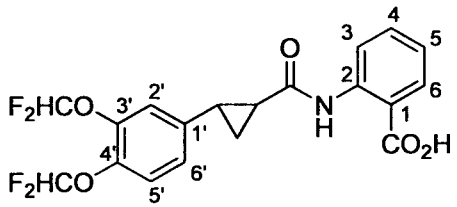
2-(3,4-bis(difluoromethoxy)phenyl)cyclopropanecarboxylic acid



Concentrated sulfuric acid (0.25 mL) was added to a solution of (*E*)-3,4-dimethoxycinnamic acid (0.50 g, 1.8 mmol) in MeOH (15 mL). The solution was heated to reflux for 16 h, cooled to rt and then quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc and the combined organic fractions were

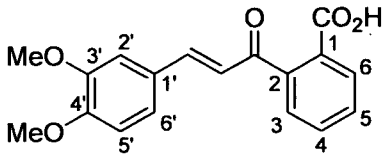
washed with water, brine, dried and concentrated providing methyl ester (0.51 g, 97%). A solution of the methyl ester (0.13 g, 0.44 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in CH_2Cl_2 (3 mL) and ether (3 mL) was treated with excess CH_2N_2. The suspension was filtered and the filtrate was concentrated. The crude residue was dissolved in MeOH (5 mL) and treated with 1 M NaOH (5 mL). The mixture was stirred at rt for 16 h and then concentrated under reduced pressure to remove the MeOH. The aqueous phase was washed with 50% EtOAc/petrol, acidified with 1 M HCl and then extracted with EtOAc. The combined organic fractions were washed with water, brine, dried and concentrated providing 2-(3,4-bis(difluoromethoxy)phenyl)cyclopropanecarboxylic acid (0.12 g, 92%) as a colourless oil; δ_H (500 MHz, DMSO-d_6) 1.38 (ddd, J = 5.0, J = 4.0, J = 2.0 Hz, 1H, CH), 1.69 (ddd, J = 2.0, J = 4.0, J = 2.0 Hz, 1H, CH), 1.89 (ddd, J = 2.0, J = 4.0, J = 2.0 Hz, 1H, CH), 2.59 (ddd, J = 2.0, J = 4.0, J = 3.0 Hz, 1H, CH), 6.49 (t, J = 73 Hz, 1H, OC*H*F_2), 6.51 (t, J = 73 Hz, 1H, OC*H*F_2), 6.97 (d, $J_{5,6}$ = 8.0, 1H, *H*6), 7.01 (s, 1H, *H*2), 7.18 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*5); δ_C (125 MHz, DMSO-d_6) 17.4, 24.0, 26.1, 115.7 (t, J = 261 Hz), 115.7 (t, J = 261 Hz), 120.6, 122.6, 124.4, 138.7, 140.9, 142.4, 179.1.

*2-(2-(3,4-bis(difluoromethoxy)phenyl)cyclopropanecarboxamido)benzoic acid (**FT112**)*



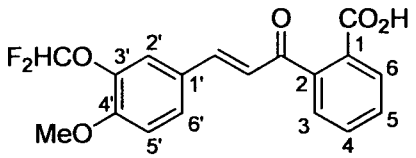
A suspension of 2-(3,4-dimethoxyphenyl)cyclopropanecarboxylic acid (0.12 g, 0.41 mmol) in CH_2Cl_2 (5 mL) was treated with oxalyl chloride (0.14 mL, 1.6 mmol). The solution was stirred at rt for 2 h and the solvent was removed under reduced pressure to give the acid chloride. Anthranilic acid (0.11 g, 82 mmol) was added to a solution of the acid chloride (0.41 mmol) in pyridine (2.0 mL) and the suspension was stirred at rt for 16 h. The solution was acidified with 1 M HCl and the resulting precipitate was collected by filtrated. The crude solid was triturated with 75% CH_2Cl_2/petrol providing 2-(2-(3,4-bis(difluoromethoxy)phenyl)cyclopropanecarboxamido)benzoic acid (90 mg, 53%) as a colourless solid; mp 177–178 °C; δ_H (500 MHz, DMSO-d_6) 1.43 (m, 1H, CH), 1.53 (m, 1H, CH), 2.09 (m, 1H, CH), 2.49 (m, 1H, CH), 6.98-7.35 (m, 6H, *H*4, *H*2', *H*5', *H*6', OC*H*F_2), 7.57 (t, $J_{4,5}$ = $J_{5,6}$ = 7.9 Hz, 1H, *H*5), 7.96 (d, $J_{3,4}$ = 7.9 Hz, 1H, *H*3), 8.42 (d, $J_{5,6}$ = 7.9 Hz, 1H, *H*6), 11.31 (s, 1H, N*H*); δ_C (125 MHz, DMSO-d_6) 16.4, 24.5, 27.7, 116.4 (t, J = 258 Hz), 116.5 (t, J = 258 Hz), 116.9, 118.6, 120.3, 121.3, 122.8, 123.9, 131.0, 133.9, 139.5, 139.9, 140.5, 142.0, 169.4, 169.7; HRMS (ESI) calculated for $C_{19}H_{15}F_4NO_5$ $[M–H]^-$ 412.0814, found 412.0808; ν_{max} 1053, 1143, 1378, 1511, 1537, 1661, 3010 cm^{-1}.

(E)-2-[3-(3,4-Dimethoxyphenyl)-1-oxo-2-propenyl]benzoic acid ***(FT114)***



A solution of 3,4-dimethoxybenzldehyde (0.37 g, 2.2 mmol) and 2-acetylbenzoic acid (0.33 g, 2.0 mmol) was dissolved in MeOH (10 mL) and treated with 50% aqueous KOH (1 mL). The mixture was heated to reflux for 16 h and then concentrated under reduced pressure to remove the MeOH. Water was added and the aqueous phase was acidified with 1 M HCl. The crude product was collected by filtration and recrystallised from EtOH providing (*E*)-2-[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]benzoic acid (0.45 g, 72%) as a yellow crystalline solid; mp 221–223 °C; δ_H (500 MHz, DMSO-d_6) 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.96 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'), 7.09 (d, J = 17.0 Hz, 1H, CH=C*H*CO), 7.13 (d, J = 17.0 Hz, 1H, C*H*=CHCO), 7.20 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*6'), 7.32 (s, 1H, *H*2'), 7.45 (d, $J_{3,4}$ = 8.0 Hz, 1H, *H*3), 7.60 (t, $J_{4,5}$ = $J_{5,6}$ = 8.0 Hz, 1H, *H*5), 7.67 (t, $J_{3,4}$ = $J_{4,5}$ = 8.0 Hz, 1H, *H*4), 7.90 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*6), 13.10 (br s, 1H, CO_2H); δ_C (125 MHz, DMSO-d_6) 55.5, 55.6, 110.5, 111.5, 123.2, 125.1, 127.0, 127.4, 129.6, 130.3, 131.8, 141.8, 144.6, 149.0, 151.1, 167.5, 195.5; HRMS (ESI) calculated for $C_{18}H_{16}O_5$ $[M+H]^+$ 313.1071, found 313.1071; ν_{max} 1138, 1251, 1584, 1707, 2844, 2913 cm^{-1}.

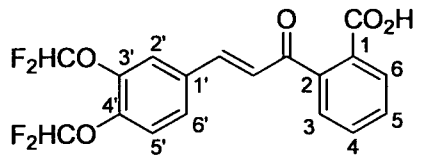
(E)-2-[3-Methoxy-4-(difluoromethoxy)phenyl)-1-oxo-2-propenyl]benzoic acid ***(FT115)***



A solution of 3,4-bis(difluoromethoxy)benzaldehyde (0.26 g, 1.1 mmol) and 2-acetylbenzoic acid (0.16 g, 1.0 mmol) was dissolved in MeOH (10 mL) and treated with 50% aqueous KOH (1 mL). The mixture was heated to reflux for 16 h and then concentrated under reduced pressure to remove the MeOH. Water was added and the aqueous phase was acidified with 1 M HCl. The crude product was collected by filtration and recrystallised from CH_2Cl_2/petrol providing (*E*)-2-[3-methoxy-4-(difluoromethoxy)phenyl)-1-oxo-2-propenyl]benzoic acid (40 mg, 11%) as a colourless solid; mp 161–168 °C; δ_H (500 MHz, DMSO-d_6) 3.90 (s, 3H, OCH_3), 7.09-7.18 (m, 4H, OC*H*F_2, CH=C*H*CO, C*H*=CHCO, *H*5'), 7.46 (d, $J_{3,4}$ = 8.0 Hz, 1H, *H*3), 7.56-7.62 (m, 3H, *H*5, *H*2', *H*6'), 7.68 (t, $J_{3,4}$ = $J_{4,5}$ = 8.0 Hz, 1H, *H*4), 7.89 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*6), 13.10 (br s, 1H, CO_2H); δ_C (125 MHz, DMSO-d_6) 56.1, 113.3, 116.6 (t, J = 256 Hz), 120.1,

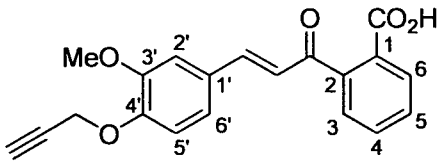
126.1, 127.2, 127.5, 127.8, 129.6, 129.8, 130.3, 130.7, 131.9, 141.6, 143.0, 152.4, 167.5, 195.3; HRMS (ESI) calculated for $C_{18}H_{14}F_2O_5$ $[M+H]^+$ 349.0882, found 349.0882; ν_{max} 1048, 1114, 1250, 1270, 1590, 1711, 2619, 2942 cm^{-1}.

(E)-2-[3,4-Bis(difluoromethoxy)phenyl)-1-oxo-2-propenyl]benzoic acid ***(FT116)***



A solution of 3,4-bis(difluoromethoxy)benzaldehyde (0.52 g, 2.2 mmol) and 2-acetylbenzoic acid (0.33 g, 2.0 mmol) was dissolved in MeOH (10 mL) and treated with 50% aqueous KOH (1 mL). The mixture was stirred at rt for 16 h and then concentrated under reduced pressure to remove the MeOH. Water was added and the aqueous phase was acidified with 25% AcOH. The crude product was collected by filtration and recrystallised from toluene/petrol providing (*E*)-2-[3,4-bis(difluoromethoxy)phenyl)-1-oxo-2-propenyl]benzoic acid (0.31 g, 40%) as a colourless crystalline solid; mp 118–119 °C; 7.18 (d, *J* = 15.6 Hz, 1H, CH=C*H*CO), 7.23 (d, *J* = 15.6 Hz, 1H, C*H*=CHCO), 7.24 (t, *J* = 73 Hz, 1H, OC*H*F_2), 7.26 (t, *J* = 73 Hz, 1H, OC*H*F_2), 7.35 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'), 7.45 (d, $J_{3,4}$ = 8.0 Hz, 1H, *H*3), 7.61-7.71 (m, 3H, *H*4, *H*5, *H*6'), 7.75 (s, 1H, *H*2'), 7.91 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*6), 13.10 (br s, 1H, CO_2H); δ_C (125 MHz, DMSO-d_6) 55.5, 55.6, 116.2 (t, *J* = 268 Hz), 116.4 (t, *J* = 268 Hz), 120.2, 120.6, 126.8, 127.5, 128.4, 129.7, 129.9, 130.2, 132.0, 132.6, 141.4, 141.6, 141.8, 143.0, 167.4, 195.5; HRMS (ESI) calculated for $C_{18}H_{12}F_4O_5$ $[M+H]^+$ 385.0694, found 385.0694; ν_{max} 1072, 1035, 1277, 1667, 1688, 2833, 3011 cm^{-1}.

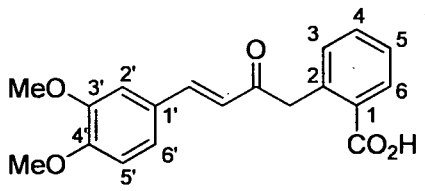
(E)-2-[3-Methoxy-4-(propargyloxy)phenyl)-1-oxo-2-propenyl]benzoic acid ***(FT117)***



A solution of 3-methoxy-4-propargyloxybenzaldehyde (0.21 g, 1.1 mmol) and 2-acetylbenzoic acid (0.16 g, 1.0 mmol) was dissolved in MeOH (10 mL) and treated with 50% aqueous KOH (1 mL). The mixture was stirred at rt for 16 h and then concentrated under reduced pressure to remove the MeOH. Water was added and the aqueous phase was acidified with 25% AcOH. The crude product was collected by filtration and recrystallised from toluene providing (*E*)-2-[3-Methoxy-4-(propargyloxy)phenyl)-1-oxo-2-propenyl]benzoic acid (0.17 g, 52%) as a colourless crystalline solid; mp 146–147 °C; δ_H

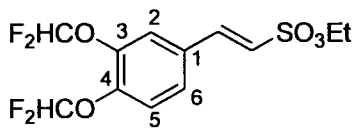
(500 MHz, DMSO-d_6) 3.67 (t, J = 2.4 Hz, 1H, C≡C*H*), 3.90 (s, 3H, OCH_3), 4.93 (d, J = 2.4 Hz, 2H, OCH_2), 7.12 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'),7.23 (s, 2H, CH=C*H*CO, C*H*=CHCO), 7.31 (dd, $J_{5',6'}$ = 8.0 Hz, $J_{2',6'}$ = 2.0 Hz), 7.45 (d, $J_{2'6'}$ = 2.0 Hz, 1H, *H*2'), 7.56 (d, $J_{3,4}$ = 8.0 Hz, 1H, *H*3), 7.70 (t, $J_{4,5}$ = $J_{5,6}$ = 8.0 Hz, 1H, *H*5), 7.78 (t, $J_{3,4}$ = $J_{4,5}$ = 8.0 Hz, 1H, *H*4), 8.00 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*6), 13.12 (br s, 1H, CO_2H); δ_C (125 MHz, DMSO-d_6) 55.7, 55.9, 78.5, 78.9, 111.0, 113.5, 122.6, 125.6, 127.4, 128.0, 129.6, 129.7, 130.3, 131.9, 141.7, 144.3, 148.7, 149.3, 167.5, 195.5; HRMS (ESI) calculated for $C_{20}H_{16}O_5$ $[M+H]^+$ 337.1070, found 337.1070; ν_{max} 1141, 1253, 1507, 1585, 1701, 2960, 3290 cm^{-1}.

(E)-2-[4-(3,4-Dimethoxyphenyl)-2-oxobut-3-enyl]benzoic acid ***(FT118)***



A solution of 3,4-dimethoxybenzldehyde (0.18 g, 1.1 mmol) and 2-(2-oxopropyl)benzoic acid (0.18 g, 2.0 mmol) was dissolved in MeOH (10 mL) and treated with 50% aqueous KOH (1 mL). The mixture was stirred at rt for 16 h and then concentrated under reduced, diluted with water and the solution was was acidified with 25% AcOH. The crude product was collected by filtration and recrystallised from toluene providing (*E*)-2-[4-(3,4-dimethoxyphenyl)-2-oxobut-3-enyl]benzoic (54 mg, 17%) as a yellow crystalline solid; mp 152–154 °C; δ_H (500 MHz, DMSO-d_6) 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.41 (s, 2H, CH_2), 6.88 (d, J = 16.0 Hz, 1H, CH=C*H*CO), 7.00 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'), 7.25-7.30 (m, 2H, *H*3, *H*6'), 7.35 (s, 1H, *H*2'), 7.37 (t, $J_{4,5}$ = $J_{5,6}$ = 8.0 Hz, 1H, *H*5), 7.51 (t, $J_{3,4}$ = $J_{4,5}$ = 8.0 Hz, 1H, *H*4), 7.51 (d, J = 16.0 Hz, 1H, C*H*=CHCO), 7.90 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*6), 12.78 (br s, 1H, CO_2H); δ_C (125 MHz, DMSO-d_6) 46.1, 55.5, 55.6, 110.4, 111.6, 123.0, 124.4, 126.7, 127.2, 130.3, 130.7, 131.7, 132.5, 137.0, 142.0, 149.0, 150.9, 168.2, 196.5; HRMS (ESI) calculated for $C_{19}H_{18}O_5$ $[M+H]^+$ 327.1227, found 327.1227; ν_{max} 1140, 1260, 1510, 1687, 2835, 2933 cm^{-1}.

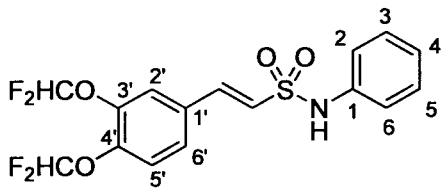
(E)-Ethyl 2-(3,4-bis(difluoromethoxy)phenyl)ethenesulfonate



A solution of 1.6 M *n*BuLi in hexane (1.6 mL, 2.5 mmol) was added to a cooled solution of ethyl diethylphosphorylmethanesulfonate (0.68 g, 2.6 mmol) in THF (25 mL) at -78 °C. The solution was stirred at -78 °C for 10 mins, warmed to at 0 °C, stirred for 10 mins and

then cooled back to -78 °C. A solution of 3,4-bis(difluoromethoxy)benzaldehyde (0.50 g, 2.1 mmol) in THF (5.0 mL) was added to the cooled mixture. The reaction was stirred at -78 °C for 1 h, warmed to 0 °C and stirred for 16 h. The reaction was quenched with water and the aqueous phase was extracted with EtOAc. The combined organic fractions were washed with water, brine, dried and concentrated. The crude residue was purified by column chromatography, eluting with 20% EtOAc/petrol, to afford (*E*)-ethyl 2-(3,4-bis(difluoromethoxy)phenyl)ethenesulfonate (0.69 g, 94%) as a colourless oil; δ_H (500 MHz, $CDCl_3$) 1.41 (t, *J* = 7.0 Hz, 3H, CH_3), 4.41 (q, *J* = 7.0 Hz, 2H, CH_2), 6.56 (t, *J* = 73 Hz, 1H, $OCHF_2$), 6.58 (t, *J* = 73 Hz, 1H, $OCHF_2$), 6.73 (d, *J* = 16.0 Hz, 1H, CH=C*H*CO), 7.32 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'), 7.39 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*6'), 7.42 (s, 1H, *H*2'), 7.54 (d, *J* = 16.0 Hz, 1H, C*H*=CHCO); δ_C (125 MHz, $CDCl_3$) 14.9, 67.1, 115.4 (t, *J* = 255 Hz), 115.5 (t, *J* = 255 Hz), 122.2, 122.4, 123.1, 126.9, 130.6, 142.0, 142.4, 144.5.

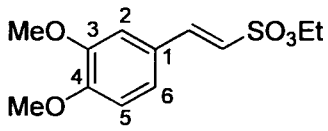
(E)-2-[3,4-Bis(difluoromethoxy)phenyl]-N-phenylethenesulfonamide ***(FT119)***



A solution of (*E*)-ethyl 2-(3,4-bis(difluoromethoxy)phenyl)ethenesulfonate (100 mg, 0.29 mmol) and tetrabutylammonium iodide (160 mg, 0.44 mmol) in acetone (5.0 mL) was heated to reflux for 16 h. The solution was concentrated under reduced pressure and dissolved in CH_2Cl_2 (5.0 mL) and triphenylphosphine (300 mg, 1.2 mmol) was added. The solution was cooled to 0 °C and sulfuryl chloride (47 µL, 0.58 mmol) was added to the reaction mixture. The solution was allowed to warm to rt and stirred for 16 h. The solvent was removed under reduced pressure and the crude chloride was purified by column chromatography, eluting with 5-20% EtOAc/petrol, providing the sulfonyl chloride (90 mg, 90%) as a colourless oil. A solution of the sulfonyl chloride (90 mg, 0.26 mmol) in CH_2Cl_2 (3.0 mL) was added to a cooled solution of aniline (52 µL, 0.58 mmol) in pyridine (2.0 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 4 h and acidified with 1 M HCl. The aqueous phase was extracted with CH_2Cl_2 and the combined organic fractions were washed with water, brine, dried and concentrated to provide (*E*)-2-[3,4-bis(difluoromethoxy)phenyl]-N-phenylethenesulfonamide (55 mg, 54%) as a dark purple coloured oil; (δ_H (500 MHz, $CDCl_3$) 6.55 (t, *J* = 73 Hz, 1H, $OCHF_2$), 6.57 (t, *J* = 73 Hz, 1H, $OCHF_2$), 6.82 (d, *J* = 16.0 Hz, 1H, CH=C*H*CO), 6.93 (s, 1H, N*H*), 7.20 (t, $J_{3,4} = J_{4,5}$ = 8.0 Hz, 1H, *H*4), 7.28-7.36(m, 7H, *H*2, *H*3, *H*5, *H*6, H2'*H*5', *H*6'), 7.43 (d, *J* = 16.0 Hz, 1H,

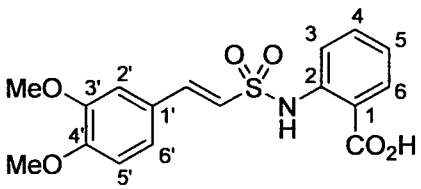
C*H*=CHCO); δ_C (125 MHz, $CDCl_3$) 115.4 (t, *J* = 255 Hz), 115.5 (t, *J* = 255 Hz), 121.1, 122.0, 122.3, 125.5, 126.0, 126.7, 129.5, 130.9, 136.1, 140.5, 142.3, 144.1; HRMS (ESI) calculated for $C_{16}H_{13}F_4NO_4S$ $[M+H]^+$ 392.0574 found 392.0575; ν_{max} 1043, 1136, 1274, 1497, 1599, 3057, 3261 cm^{-1}.

(E)-Ethyl 2-(3,4-dimethoxyphenyl)ethenesulfonate



A solution of 1.6 M *n*BuLi in hexane (1.4 mL, 2.2 mmol) was added to a cooled solution of ethyl diethylphosphorylmethanesulfonate (0.58 g, 2.2 mmol) in THF (25 mL) at -78 °C. The solution was stirred at -78 °C for 10 mins, warmed to at 0 °C, stirred for 10 mins and then cooled back to -78 °C. A solution of 3,4-dimethoxybenzaldehyde (0.30 g, 1.8 mmol) in THF (5.0 mL) was added to the cooled mixture. The reaction was stirred at -78 °C for 1 h, warmed to 0 °C and stirred for 16 h. The reaction was quenched with water and the aqueous phase was extracted with EtOAc. The combined organic fractions were washed with water, brine, dried and concentrated. The crude residue was purified by column chromatography, eluting with 20% EtOAc/petrol, to afford (*E*)-ethyl 2-(3,4-dimethoxyphenyl)ethenesulfonate (0.47 g, 96%) as a colourless crystalline solid; δ_H (500 MHz, $CDCl_3$) 1.40 (t, *J* = 7.0 Hz, 3H, C*H*$_3$), 3.92 (s, 3H, OC*H*$_3$), 3.93 (a, 3H, OC*H*$_3$), 4.22 (q, *J* = 7.0 Hz, 2H, C*H*$_2$), 6.59 (d, *J* = 16.0 Hz, 1H, CH=C*H*CO), 6.90 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'), 7.00 (s, 1H, *H*2'), 7.11 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*6'), 7.53 (d, *J* = 16.0 Hz, 1H, C*H*=CHCO); δ_C (125 MHz, $CDCl_3$) 14.9, 55.9, 56.0, 66.6, 109.9, 111.1, 118.5, 123.3, 124.8, 144.6, 149.4, 152.0.

(E)-2-(2-(3,4-Dimethoxyphenyl)vinylsulfonamido)benzoic acid ***(FT120)***



A solution of (*E*)-ethyl 2-(3,4-dimethoxyphenyl)ethenesulfonate (200 mg, 0.73 mmol) and tetrabutylammonium iodide (320 mg, 1.1 mmol) in acetone (10 mL) was heated to reflux for 16 h. The solution was concentrated under reduced pressure and the sodium salt was dissolved in CH_2Cl_2 (5.0 mL) and added to a cooled solution of sulfuryl chloride (210 µL, 2.6 mmol) and triphenylphosphine (710 mg, 3.1 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C. The solution was allowed to warm to rt and stirred for 16 h. The solvent was removed under

reduced pressure and the crude chloride was purified by column chromatography, eluting with 20% EtOAc/petrol, providing the sulfonyl chloride (150 mg, 78%) as a yellow oil. A solution of the sulfonyl chloride (150 mg, 0.57 mmol) in CH_2Cl_2 (2.0 mL) was added to a cooled solution of anthranilic acid (160 mg, 1.14 mmol) in pyridine (2.0 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 16 h and diluted with water. The aqueous phase was ashed with 50% EtOAc/petrol and the organic phase was discarded. The aqueous phase was acidified with 1 M HCl and extracted with CH_2Cl_2. The combined organic fractions were washed with water, brine, dried and concentrated. The crude product was recrystallised from CH_2Cl_2 to provide (*E*)-2-(2-(3,4-dimethoxyphenyl)vinylsulfonamido)benzoic acid (30 mg, 14%) as a colourless crystalline solid; mp 194–196 °C; δ_H (400 MHz, $CDCl_3$) 3.88 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 6.70 (d, J = 16.0 Hz, 1H, CH=C*H*CO), 6.84 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*5'), 6.94 (s, 1H, *H*2'), 7.05 (d, $J_{5',6'}$ = 8.0 Hz, 1H, *H*6'), 7.11 (t, $J_{3,4} = J_{4,5}$ = 8.0 Hz, 1H, *H*4), 7.57 (t, $J_{4,5} = J_{5,6}$ = 8.0 Hz, 1H, *H*5), 7.58 (d, J = 16.0 Hz, 1H, C*H*=CHCO), 7.72 (d, $J_{3,4}$ = 8.0 Hz, 1H, *H*3), 8.10 (d, $J_{5,6}$ = 8.0 Hz, 1H, *H*6), 10.36 (s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 55.9, 56.0, 109.9, 111.1, 114.0, 117.9, 121.9, 122.6, 123.3, 124.9, 132.3, 135.7, 141.2, 143.5, 149.3, 151.9, 171.5; HRMS (ESI) calculated for $C_{17}H_{17}NO_6S$ $[M–H]^-$ 362.0704, found 362.0699; ν_{max} 1136, 1267, 1513, 1682, 2975, 3277 cm^{-1}.

Proline Incorporation

A well-characterized cloned rat mesangial cell line [30] (gift of D Nikolic-Patterson) is cultured in DMEM with FBS, 100U/mL penicillin, and 100ug/mL streptomycin in a humidified 5% CO_2 atmosphere at 37°C. Cells are plated into 24-well culture dishes in DMEM/10%FBS at low density and allowed to adhere overnight. Cells are used between passages 20 and 40. The subconfluent cells are starved overnight in DMEM/0.1%FBS containing 150uM L-ascorbic acid, prior to 4 hours of pre-treatment with or without tranilast or the FT compounds, followed by the addition of 5ng/mL rhTGF-$\beta_1$1 (R&D Systems) and 1uCi/mL of L-(2,3,4,5-^{3}H)-proline. Control wells have the compounds but no TGF-β_1 added. Cells are incubated for a further 44 hours during which time their appearance is visually monitored. The cells are then washed three times in ice-cold PBS, twice in ice cold 10% TCA and solubilized in 750uL 1M NaOH for 45 minutes at 37°C or overnight at 4°C. A 500uL aliquot is neutralized with 500uL 1M HCl and 10mL scintillation fluid (Instagel Plus – Perkin-Elmer) added. Counts are performed on a beta counter.

To normalize the proline incorporation counts to take into account the proliferative effects

of TGF-β_1, a BioRad protein assay is performed on a 100-150uL aliquot of the remaining solubilized cells. The sample is neutralized with an equal amount of 1M HCl prior to the assay. The BSA standards used to construct the standard curve have the same amount of 1M NaOH and 1M HCl added as is present in the samples for assay.

Proline incorporation is expressed as cpm/ug protein. In order to compare inter-assay results, the incorporation is expressed as percentage reduction of TGF stimulated proline incorporation, where TGF alone gives 0% reduction and the zero control gives 100% reduction.

Mesangial cells

Compounds in **bold** have minimal effect on cell appearance and viability

N.B suppressed MTT result indicates reduced cell viability

Analogue	**Formula Mol. Wt.**	**% reduction of TGF stimulation _proline inc.**	**Mesangial Cell Assay TGF Collagen Synthesis**	**Effect on mesangial cell appearance**
1	Tranilast $C_{18}H_{17}NO_5$ 327.33	~20-50% @30μm 50-70% @ 100μM	=T	OK, some stress @ 100μM
101	$C_{18}H_{23}NO_5$ 333.38	No effect	<T	OK
103	$C_{17}H_{16}N_2O_5$ 328.32	No effect	<T	sick @ 30uM Ppt @ 100uM
104	$C_{17}H_{16}N_2O_5$ 328.32	No effect	<T	OK
111	$C_{19}H_{19}NO_5$ 341.36	15%@30uM 70%@100uM	~T	OK
112	$C_{19}H_{15}F_4NO_5$ 413.32	70%@10uM >10uM-Toxic effect	>T	sick@10uM, dead@30uM
114	$C_{18}H_{16}O_5$ 312.32	No effect	<T	OK
115	$C_{18}H_{14}F_2O_5$ 348.30	No effect	<T	dead@ 100uM
116	$C_{18}H_{12}F_4O_5$ 384.28	No effect	<T	sick@30uM dead@100uM

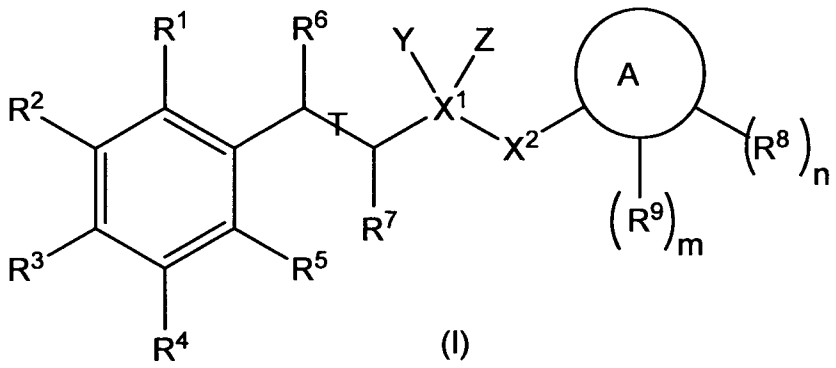
Analogue	Formula Mol. Wt.	% reduction of TGF stimulation _proline inc.	Mesangial Cell Assay TGF Collagen Synthesis	Effect on mesangial cell appearance
117	$C_{20}H_{16}O_5$ 336.34	No effect	<T	sick@30uM dead@100uM
118	$C_{19}H_{18}O_5$ 326.34	No effect	<T	sick@100uM
119	$C_{16}H_{13}F_4NO_4S$ 391.34	No effect	<T	sick@30uM dead@100uM
120	$C_{17}H_{17}NO_6S$ 363.38	No effect	<T	dying@100uM

Ppt - compound precipitated during the assay.

The details of specific embodiments described in this invention are not to be construed as limitations. Various equivalents and modifications may be made without departing from the essence and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

CLAIMS

1. A compound of Formula (I)



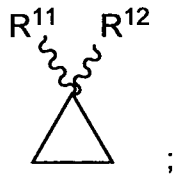
(I)

or a pharmaceutically acceptable drug or prodrug thereof,

wherein;

$X^1(YZ)$ is C=O, $C(F_2)$ or SO_2;

X^2 is NR^{10} or $(CH_2)_p$;

T is a double bond, a triple bond or when T is a single bond, one pair of R^6 and R^7 are fused to form a cyclopropane ring of the formula  ;

A is selected from the group consisting of C_3 to C_{12} cycloalkyl, C_3 to C_{12} cycloalkenyl, C_1 to C_{12} heterocycloalkyl, C_1 to C_{12} heterocycloalkenyl, C_6-C_{18} aryl and C_6 to C_{18} heteroaryl;

R^1, R^4, and R^5 are each independently selected from the group consisting of: H, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12}

heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{13}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}R^{14}$, and acyl;

R^2 and R^3, are each independently selected from the group consisting of: H, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{13}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}R^{14}$ and acyl; or
R^2 and R^3 may be fused to form a 5 or 6 membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring each of which may be optionally substituted;

one pair of R^6 and R^7 are present when T is a double bond but R^6 and R^7 are not present when T is a triple bond, each R^6 and R^7 being independently selected from the group consisting of: H, NO_2, CN, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted C_2-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, optionally substituted C_1-C_{18} heteroaryl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{14}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}R^{14}$, and acyl;

R^8 is selected from the group consisting of H, halogen, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$, SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{13}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$ and $NR^{13}R^{14}$ and acyl;

R^9 is selected from the group consisting of OH, OR^{13}, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, tetrazol-5-yl, SO_2R^{13}, $SO_2NR^{13}R^{14}$ and $CONHOR^{13}$;

R^{10} is selected from the group consisting of H, a N-protecting group, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} heterocycloalkyl, optionally substituted C_1-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

R^{11} and R^{12} are independently selected from the group consisting of H, halogen, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted C_2-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18} aryl, optionally substituted C_1-C_{18} heteroaryl, optionally substituted C_1-C_{12} alkyloxy, optionally substituted C_2-C_{12} alkenyloxy, optionally substituted C_2-C_{12} alkynyloxy, optionally substituted C_1-C_{10} heteroalkyloxy, optionally substituted C_3-C_{12} cycloalkyloxy, optionally substituted C_3-C_{12} cycloalkenyloxy, optionally substituted C_1-C_{12} heterocycloalkyloxy, optionally substituted C_1-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18} aryloxy, optionally substituted C_1-C_{18} heteroaryloxy, optionally substituted C_1-C_{12} alkylamino, SR^{13}, SO_3H, $SO_2NR^{13}R^{14}$,

SO_2R^{13}, $SONR^{13}R^{14}$, SOR^{13}, COR^{13}, COOH, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}COR^{14}$, $NR^{13}COOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}CONR^{14}R^{15}$, $NR^{13}R^{14}$, and acyl;

each R^{13}, R^{14}, R^{15} are each independently selected from the group consisting of H, -OH, optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{10} heteroalkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted C_1-C_{12} heterocycloalkyl, optionally substituted C_1-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

n is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

m is an integer selected from the group consisting of 1, 2, 3, and 4;

m + n is an integer selected from the group consisting of 1, 2, 3, 4, and 5; and

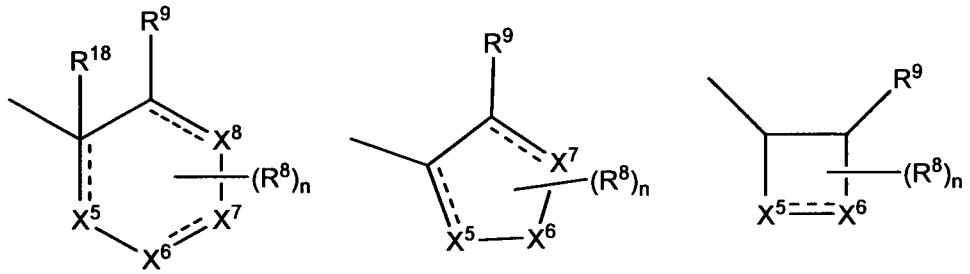
p is an integer selected from the group consisting of 0, 1, 2, 3, 4, and 5;

and when $X^1(YZ)$ is $C(F_2)$ or SO_2; or
when T is a cyclopropane ring as defined above; or
when R^1 and R^5 are H and T is a double bond; or
when X^2 is $(CH_2)_p$ and p is 0 or 1; or
when A is selected from the group consisting of C_3 to C_{12} cycloalkyl, preferably C_4 to C_6 cycloalkyl, C_1 to C_{12} heterocycloalkenyl, and C_6 to C_{18} heteroaryl;
then R^2 and R^3 may also be independently selected from $-X^3$-R^{16} or $-X^4$-R^{17};

wherein X^3 and X^4 may be the same or different and are selected from the group consisting of a bond C, O, N and S; and

R^{16} and R^{17} may be the same or different and are selected from the group consisting of H, NHR^{13}, $NR^{13}R^{14}$, OR^{13}, halogen, C_1 to C_{10} alkyl, C_3 to C_{10} cyclokalkyl, C_3 to C_{10} cycloalkylmethyl, C_3 to C_{10} alkene, C_3 to C_{10} alkyne, aryl, C_5 to C_{20} alkaryl, fused C_5 to C_{20} aryl or alkaryl and a hydrocarbon chain containing a heterocyclic or fused ring, any of which may be optionally substituted;

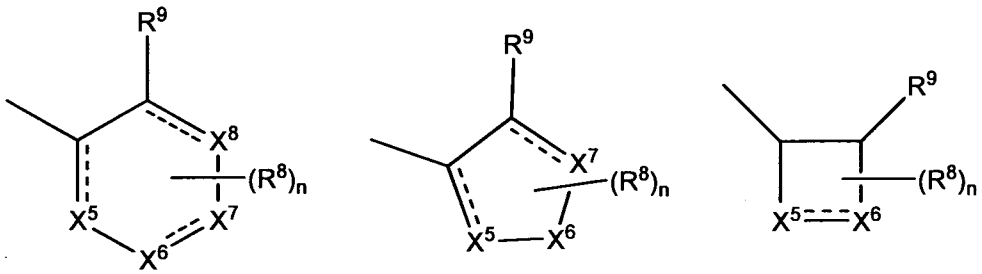
providing that when $X^1(YZ)$ is C=O, X^2 is NH and T is a double bond then A has the general formula:



wherein X^5, X^6, X^7 and X^8 may be independently C, S, O or N;
R^{18} is absent, H or $COOR^{13}$ and R^9 can be H when R^{18} is $COOR^{13}$, more preferably COOH;
but A cannot be phenyl and R^1 to R^5 cannot be $-CF_3$;

and further providing that when $X^1(YZ)$ is C=O, X^2 is NH and T is a cyclopropane ring as defined above then R^9 cannot be tetrazol-5-yl; and

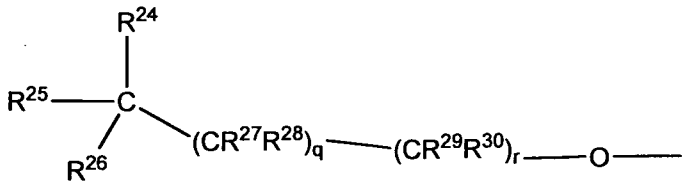
and even further providing that when $X^1(YZ)$ is SO_2, then A has the general formula:



wherein X^5, X^6, $X^7$and X^8 may be independently C, S, O or N and R^9 can be H when R^2 and R^3 are each independently a C_1-C_{12} alkyloxy group containing at least one halogen atom, and more preferably when R^2 and R^3 are each $-OCHF_2$.

2. A compound according to claim 1, wherein at least one of R^1, R^2, R^3, R^4, and R^5 is selected from the group consisting of a C_1-C_{12} alkyloxy containing at least one halogen atom, a C_1-C_{12} alkenyloxy containing at least one halogen atom, and a C_1-C_{12} alkynyloxy containing at least one halogen atom.

3. A compound according to claim 2, wherein the C_1-C_{12} alkyloxy group is of Formula (A):



Formula (A)

- wherein: R^{24}, R^{25}, and R^{26} are each independently selected from the group consisting of: H, halogen, OH, NO_2, CN, NH_2, optionally substituted C_1-C_{12} alkyl, and optionally substituted C_2-C_{12} alkenyl;
- R^{27}, R^{28}, R^{29}, and R^{30} are each independently selected from the group consisting of: H, halogen, OH, NO_2, CN, and NH_2;
- at least one of R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, and R^{30} is or contains a halogen atom;
- q is an integer selected from the group consisting of: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and
- r is an integer selected from the group consisting of: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

4. A compound according to claim 3, wherein q and r are 0, and at least two of R^{24}, R^{25}, and R^{26} are a halogen.

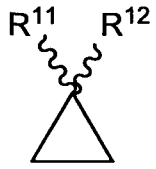
5. A compound according to any one of claims 1 to 4, wherein the halogen is fluorine.

6. A compound according to claim 1, wherein at least one of R^1, R^2, R^3, R^4, and R^5 is selected from the group consisting of–O-CHF_2, -O-CF_3, -OCF_2CHF_2.

7. A compound according to any one of claims 1 to 6, wherein T is a double bond.

8. A compound according to any one of claims 1 to 6, wherein T is a triple bond.

9. A compound according to any one of claims 1 to 6, wherein T is a single bond and one pair of R^6 and R^7 are fused to form a cyclopropane ring of the formula



10. A compound according to any one of claims 1 to 9, wherein R^2 and R^3 form a bridging difluoromethylenedioxy group or a bridging tetrafluoroethylenedioxy group.

11. A compound according to any one of claims 1 to 10 wherein R^6 is CH_3.

12. A compound according to any one of claims 1 to 11 wherein R^7 is CH_3 or CN.

13. A compound according to any one of claims 1 to 12, wherein R^8 is either H or Me.

14. A compound according to any one of claims 1 to 13 wherein m is 1 and R^9 is selected from COR^{13} and $CONR^{13}R^{14}$.

15. A compound according to claim 14 wherein R^9 is selected from the group consisting of COOH, $CONH_2$, CONHOH and $CONHCH_3$.

16. A compound according to any one of claims 1 to 13 wherein R^9 is the group tetrazol-5-yl.

17. A compound according to any one of claims 1 to 13 wherein R^9 is selected from the group consisting of SO_2R^{13}, $SO_2NR^{13}R^{14}$.

18. A compound according to claim 17 wherein R^9 is selected from the group consisting of SO_2Me, SO_2NH_2, SO_2NHMe, SO_2NMe_2.

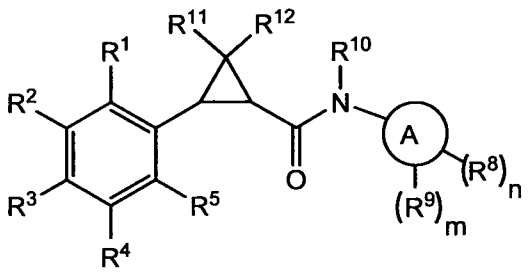
19. A compound according to any one of claims 1 to 13, wherein R^9 is $NR^{13}R^{14}$.

20. A compound according to claim 19, wherein R^9 is NH_2.

21. A compound according to any one of claims 1 to 20, wherein R^8 is a halogen.

22. A compound according to any one of claims 1 to 21, wherein X^2 is NH.

23. A compound having the formula (IIa)

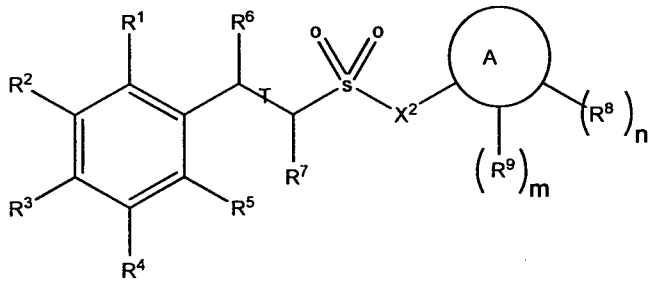


(IIa)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

A, R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, R^{11} and R^{12} are as defined in claim 1.

24. A compound having the formula (III)

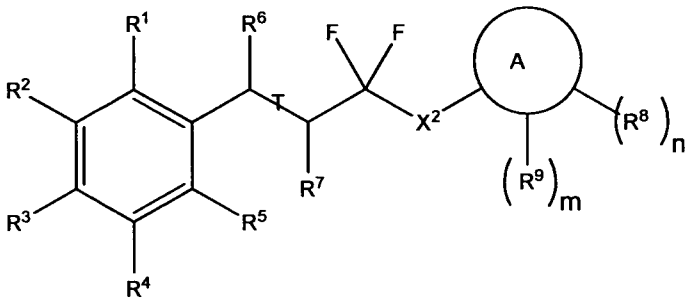


(III)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

A, T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and X^2 are as defined in claim 1.

25. A compound of the formula Formula (IV)

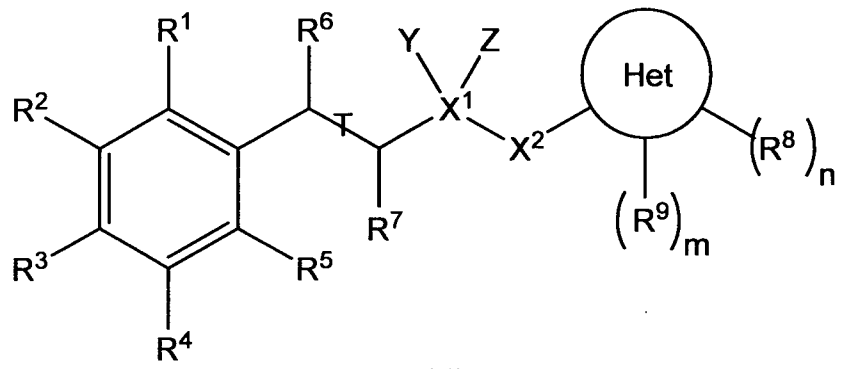


(IV)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

A, T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and X^2 are as defined in claim 1.

26. A compound having the Formula (V)

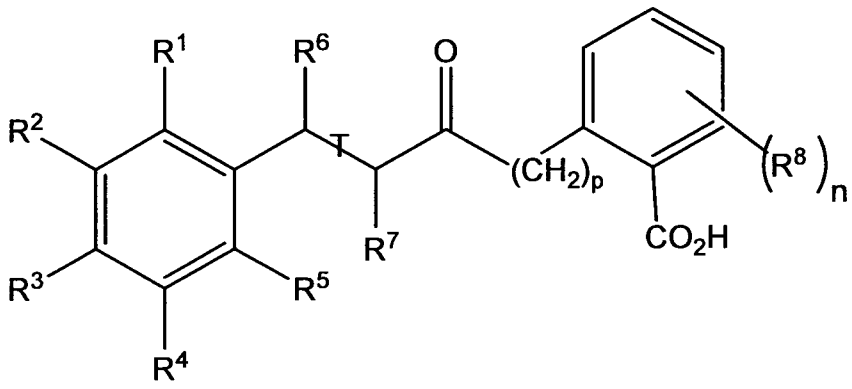


(V)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $X^1(YZ)$ and X^2 are as defined in claim 1 and Het represents a heterocyclic ring.

27. A compound of formula (VI)



(VI)

or a pharmaceutically acceptable salt or prodrug thereof, wherein;

T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and p are as defined in claim 1.

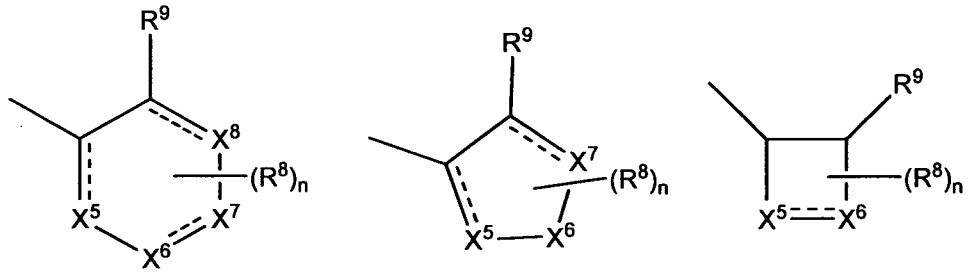
28. The compound of any one of claims 23 to 27 wherein R^6 and R^7 are H.

29. The compound of any one of claims 23 to 28, wherein R^{11} and R^{12} are selected from H, halogen, or CN.

30. The compound of any one of claims 23 to 29 wherein R^9 is selected from CO_2H, CO_2R^{13}, SO_2R^{13}, SO_2NH_2, $SONHR^{13}$, $SONR^{13}_2$ and 5-tetrazolyl.

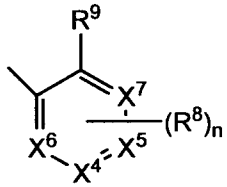
31. The compound of any one of claims 23 to 30, wherein, R^1 and R^5 are H and R^2 and R^3 are O-R^{16} and O-R^{17}, wherein R^{16} and R^{17} are independently and preferably selected form the group consisting of unsubstituted C_1-C_6 alkyl, preferably methyl or ethyl; C_1-C_6 fluoro substituted alkyl, preferably, F_3CO, F_2HCO, F_2HCF_2CO; or are fused to form a 5 or 6 membered ring, preferably a fluoro substituted 1,4-dioxane or a fluoro substituted 1,3-dioxolane; or a C_1 to C_6 alkenyl, preferably $-CH_2CCH$.

32. The compound of any one of claims 23 to 31, wherein A has the general formula selected from the group consisting of



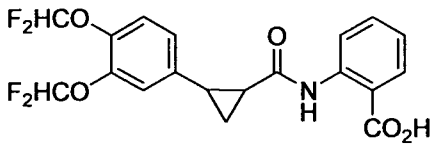
wherein X^5, X^6, $X^7$and X^8 may be independently C, S, O or N.

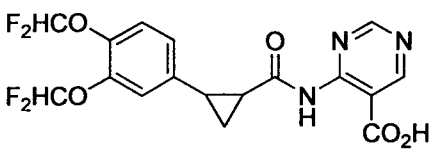
33. The compound of claim 32, wherein A has the general formula

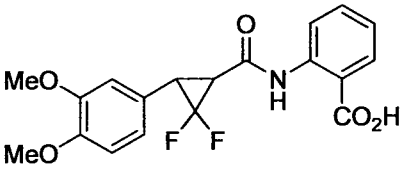


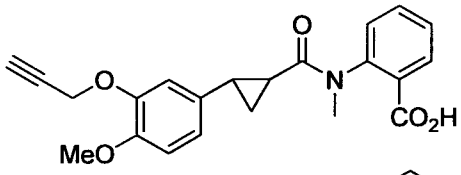
wherein X^4, X^5, X^6 and X^7 may be C or N.

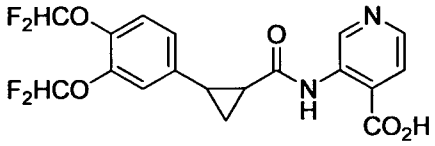
34. A compound selected from the group consisting of

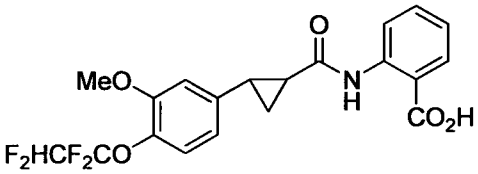


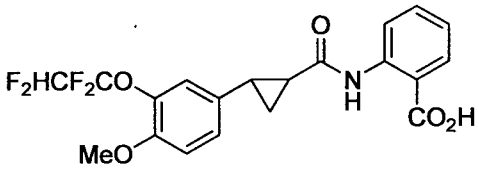


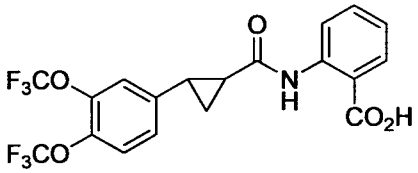


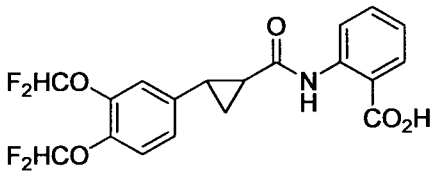


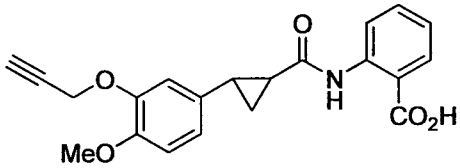


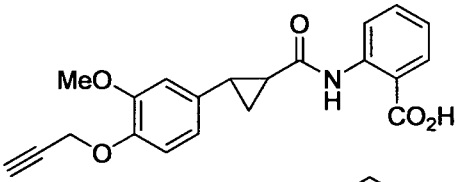


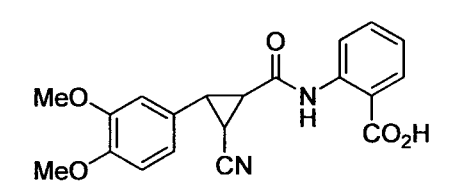


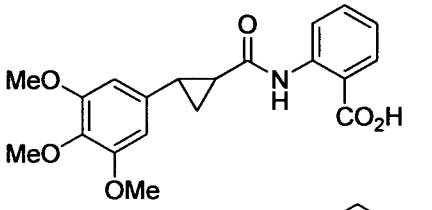


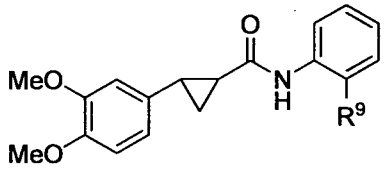


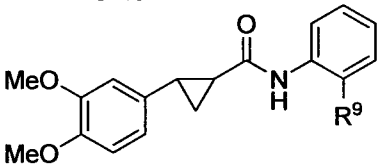






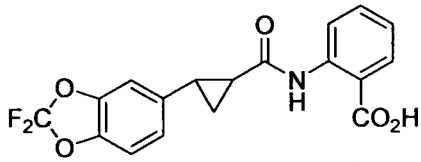


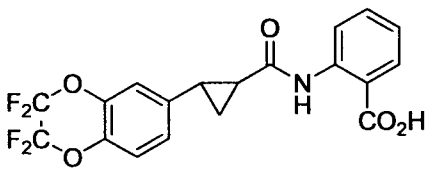


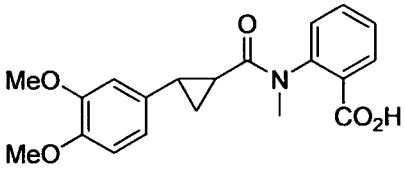


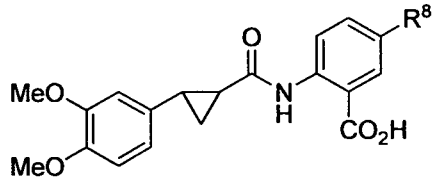
R9 = NH2, CONH2, CONHMe, CONHOH

R9 = SO2Me, SO2NH2



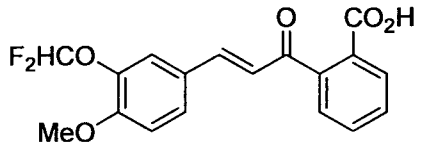


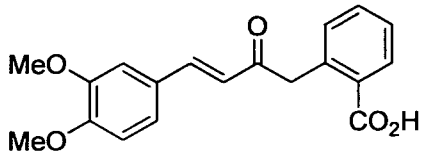


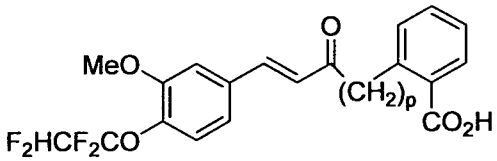


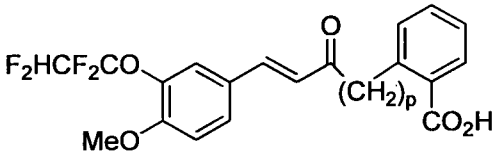
R8 = Hydrogen, Halogen

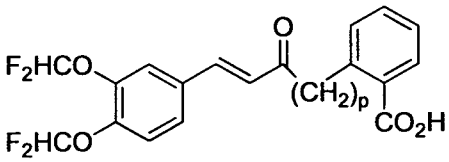
35. A compound selected from the group consisting of

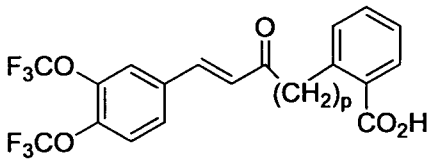


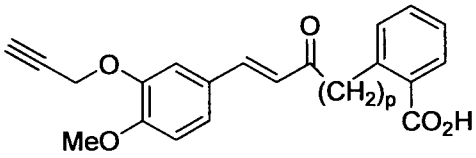


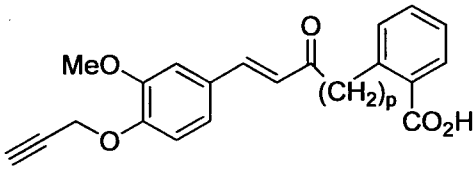


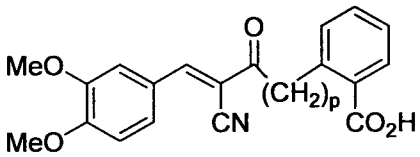


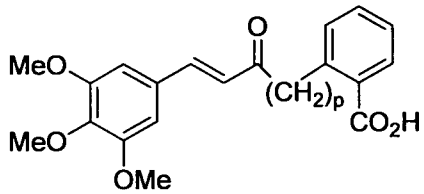


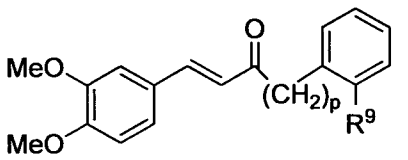




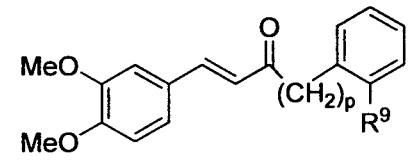




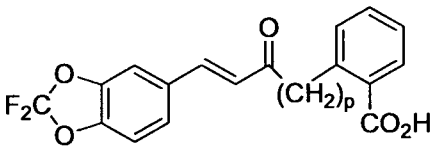


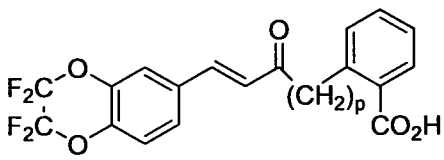


R^9 = SO_2Me, SO_2NH_2, 5-tetrazolyl



R^9 = NH_2, $CONH_2$, CONHMe, CONHOH

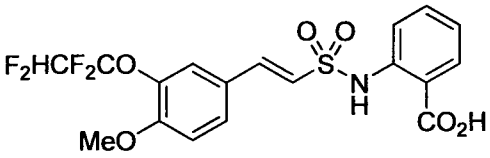


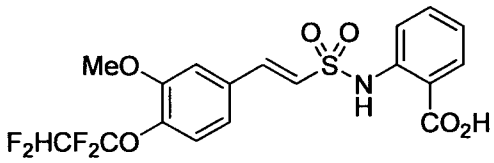


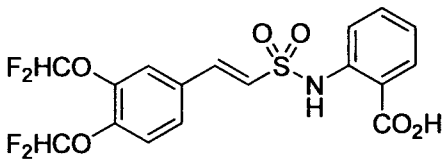
wherein p is 0 or 1.

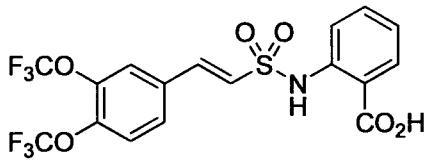
5

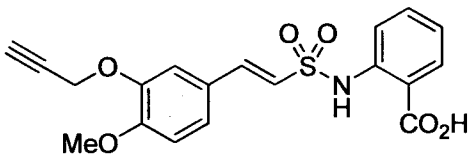
36. A compound selected from the group consisting of

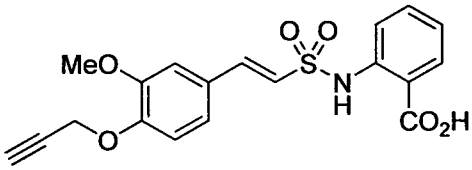


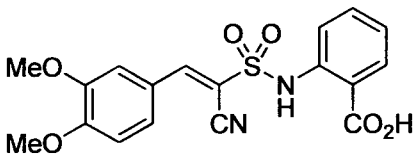


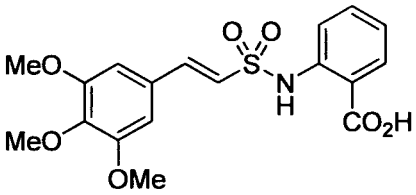


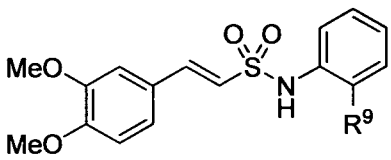


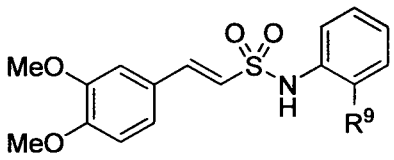






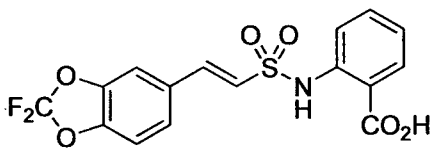


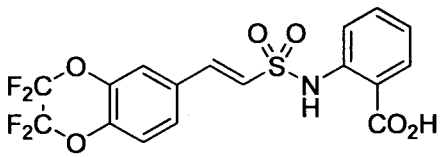


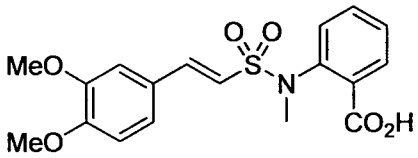


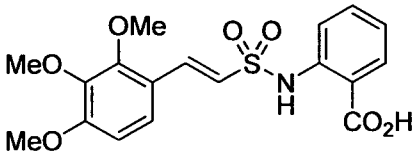
R^9 = SO_2Me, SO_2NH_2, 5-tetrazolyl

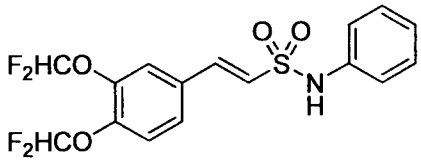
R^9 = NH_2, $CONH_2$, CONHMe, CONHOH

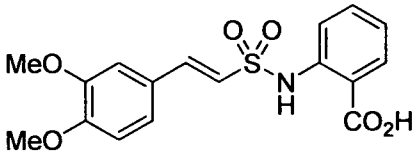




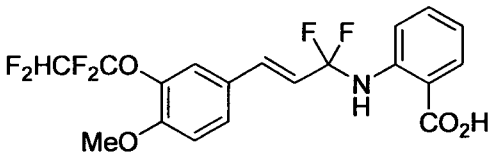


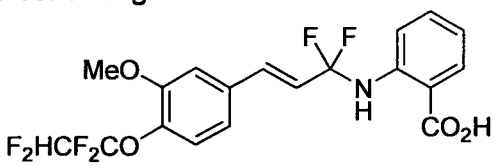


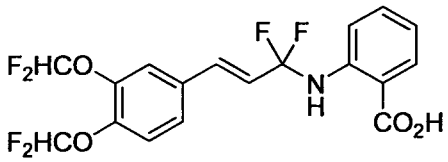


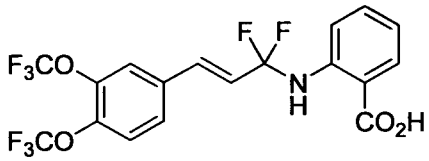


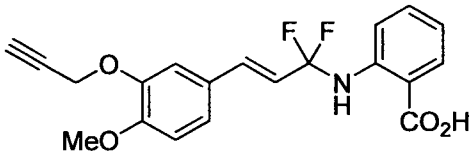
37. A compound selected from the group consisting of

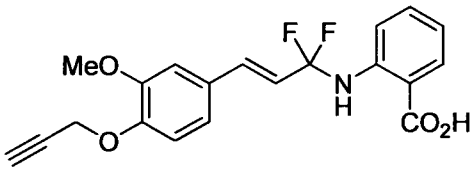


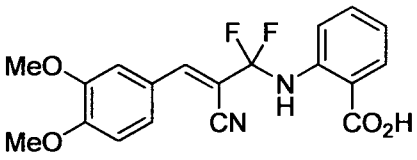


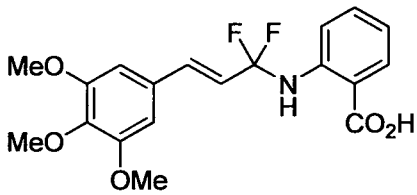


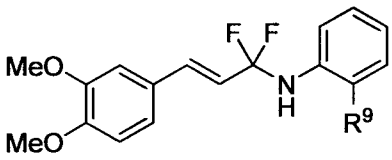


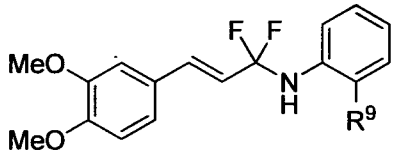






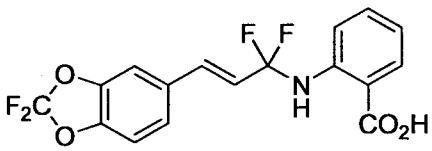


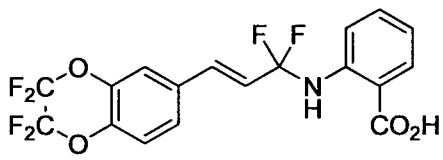


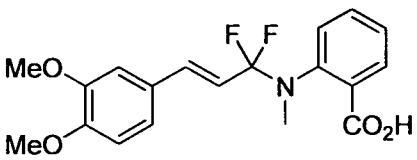


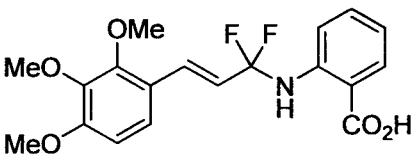
R^9 = SO_2Me, SO_2NH_2, 5-tetrazolyl

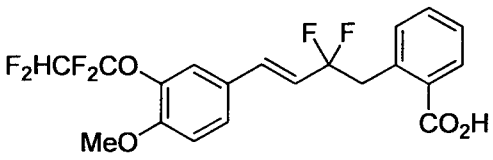
R^9 = NH_2, $CONH_2$, CONHMe, CONHOH

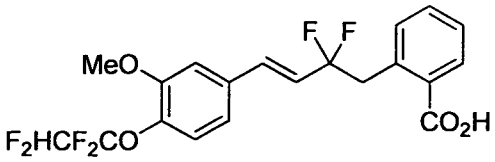


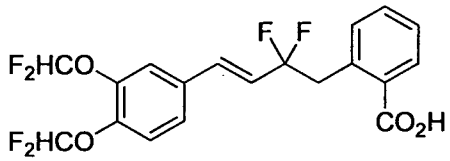


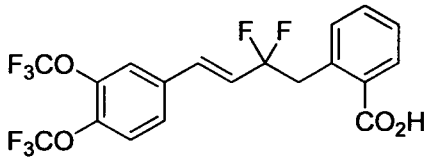


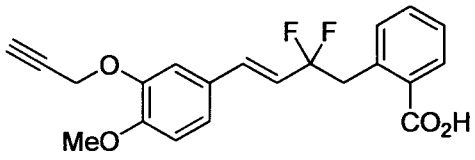


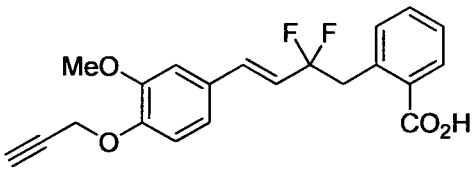


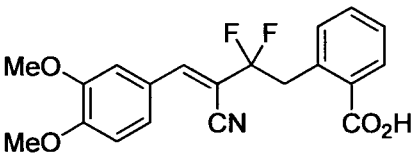


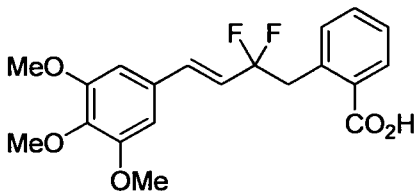


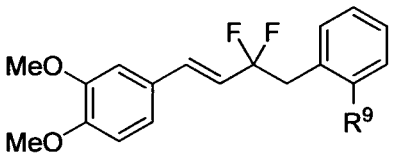


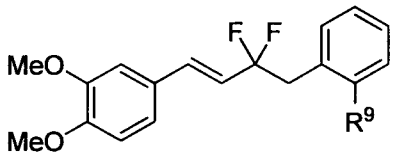






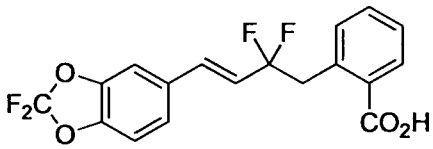


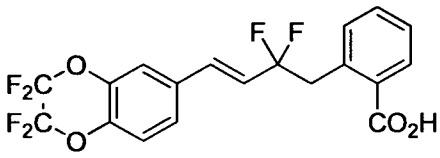


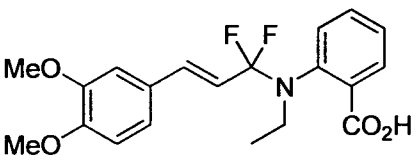


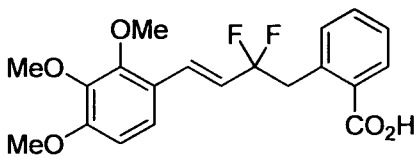
R^9 = SO_2Me, SO_2NH_2, 5-tetrazolyl

R^9 = NH_2, $CONH_2$, CONHMe, CONHOH

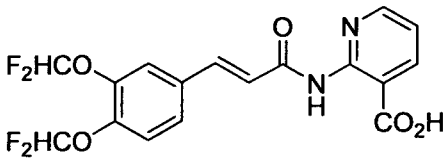


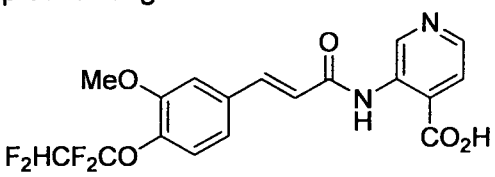


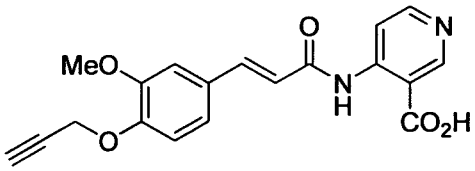


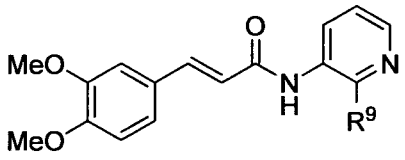


38. A compound selected from the group consisting of

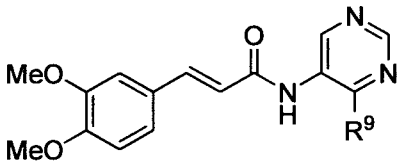


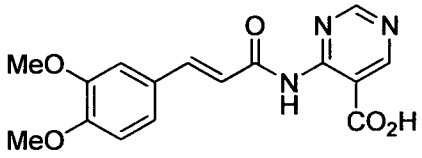




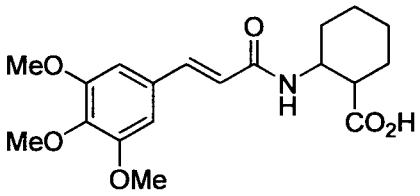


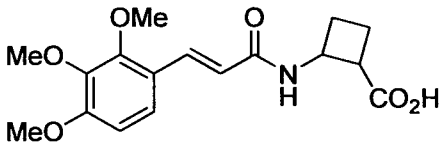
R^9 = NH_2, $CONH_2$, CONHMe, CONHOH

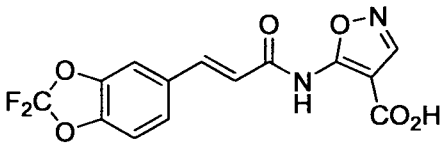


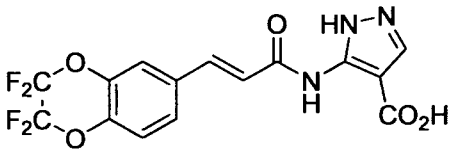


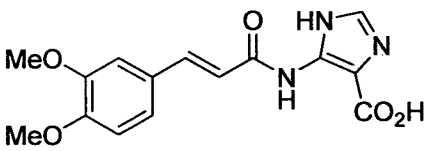
R^9 = SO_2Me, SO_2NH_2, SONHMe, $SONMe_2$

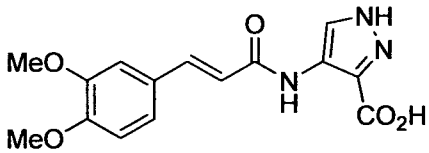


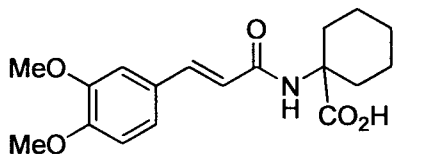


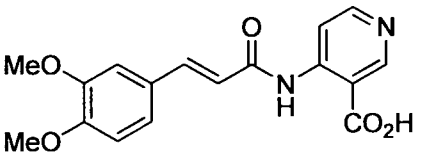


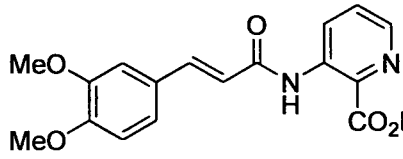






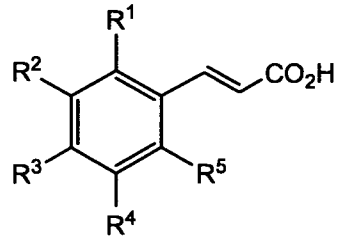




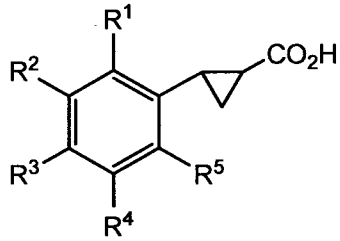


39. A method for the preparation of a compound of formula (IIa) according to claim 23, the method including

(a) cyclopropanation of a compound of the formula

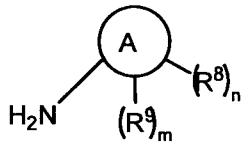


to obtain a compound of the formula

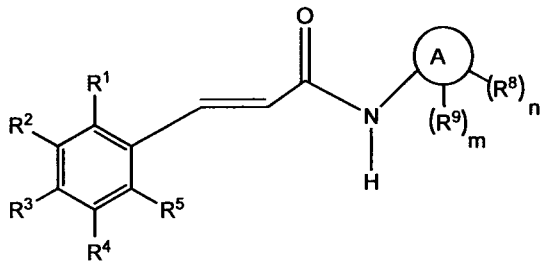


and

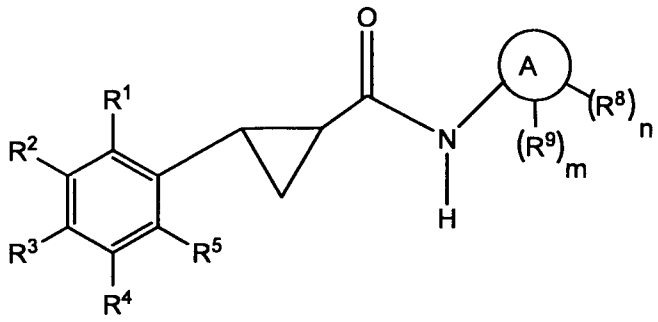
(b) condensing the compound obtained in step (a) with a compound of formula



40. A method for preparing a compound of formula (IIa) according to claim 23 including cyclopropanation of a compound of the formula

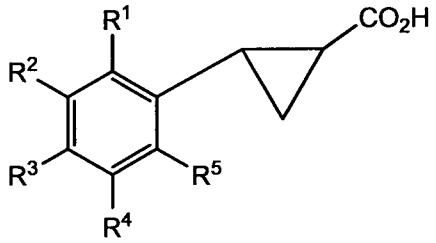


to obtain a compound of formula

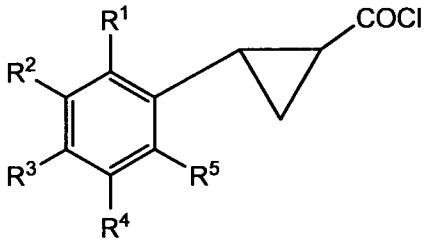


41. A method of preparing a compound of Formula (IIa) according to claim 23 including the steps of

(a) reacting a compound of the formula

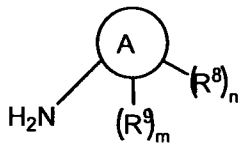


to obtain an acid chloride of the formula



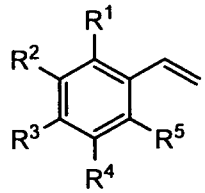
and

(b) condensing the acid chloride prepared in step (a) with a compound of the formula

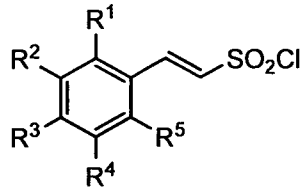


42. A method for the preparation of a compound of formula (III) according to claim 24 including the steps of

(a) reacting a terminal alkene of the formula

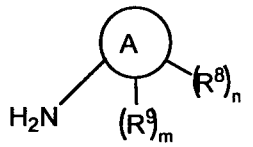


to provide a sulfonyl chloride compound of the formula



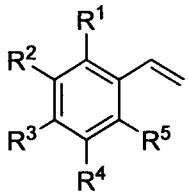
and

(b) condensing the sulfonyl chloride prepared in step (a) with a compound of formula

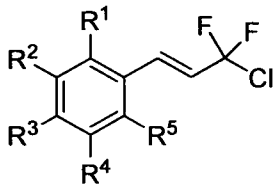


43. A method for the preparation of a compound of formula (IV) according to claim 25 in which X^2 is NH that includes the steps of;

(a) reacting a terminal alkene of the formula

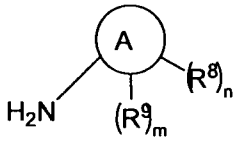


to provide a compound of formula



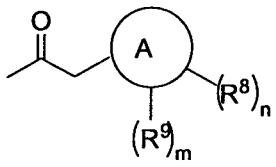
and

(b) condensing the compound prepared in step (a) with a compound of the formula

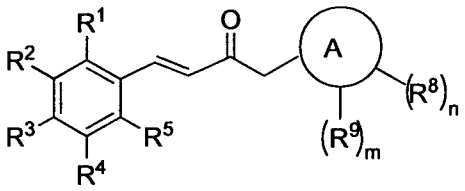


44. A method for the preparation of compounds of formula (IV) according to claim 25 in which X^2 is CH_2 that includes the steps of

(a) reacting a compound of the formula

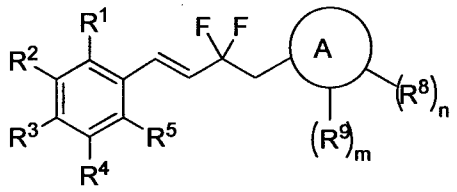


to provide a ketone of the formula



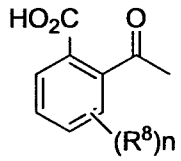
and

(b) converting the ketone prepared in step (a) to a compound of the formula

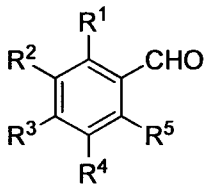


45. A method of preparing a compound of formula (VI) according to claim 27 where p is 0, including the step of

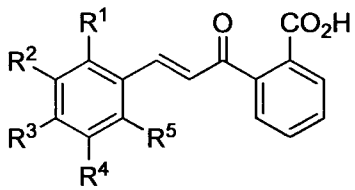
reacting a compound of the formula



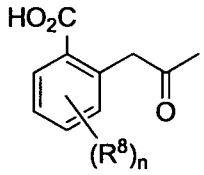
with a compound of the formula



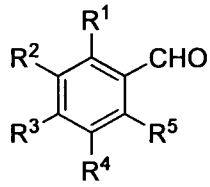
to obtain a compound of the formula



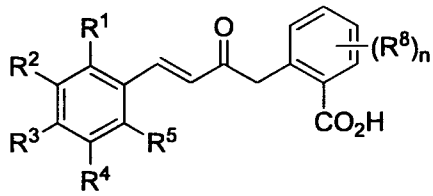
46. A method of preparing a compound of formula (VI) according to claim 27 where p is 1, including the step of reacting a compound of formula



with a compound of formula



to provide a compound of formula



47. Use of a compound according to any one of claims 1 to 38 for the treatment or prevention of diseases associated with fibrosis.

48. Use of a compound according to any one of claims 1 to 38 in the preparation of a medicament for the treatment or prevention of diseases associated with fibrosis.

49. A compound according to any one of claims 1 to 38 substantially as hereinbefore described with reference to the examples.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/000745

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07C 65/40 (2006.01)	*C07C 235/40* (2006.01)	*C07C 235/68* (2006.01)	*C07C 217/80* (2006.01)	*C07C 235/42* (2006.01)
C07C 225/22 (2006.01)	*C07C 235/84* (2006.01)	*C07C 229/56* (2006.01)	*C07C 217/62* (2006.01)	*C07C 237/30* (2006.01)
C07C 229/56 (2006.01)	*C07C 235/36* (2006.01)	*C07C 317/22* (2006.01)	*C07C 311/13* (2006.01)	*C07C 317/36* (2006.01)
C07C 311/35 (2006.01)	*C07C 317/38* (2006.01)	*C07C 311/39* (2006.01)	*C07C 317/46* (2006.01)	*C07C 311/16* (2006.01)
C07D 317/46 (2006.01)	*C07D 319/20* (2006.01)	*C07D 257/04* (2006.01)	*C07D 213/80* (2006.01)	*C07D 213/79* (2006.01)
C07D 213/75 (2006.01)	*C07D 213/81* (2006.01)	*C07D 239/47* (2006.01)	*C07D 239/28* (2006.01)	*C07D 413/12* (2006.01)
C07D 405/12 (2006.01)	*C07D 233/90* (2006.01)	*A61K 31/165* (2006.01)	*A61K 31/196* (2006.01)	*A61K 31/44* (2006.01)
A61K 31/18 (2006.01)	*A61K 31/435* (2006.01)	*A61K 31/195* (2006.01)	*A61K 31/4353* (2006.01)	*A61P 1/16* (2006.01)
A61P 11/00 (2006.01)	*A61P 9/00* (2006.01)	*A61P 13/12* (2006.01)	*A61P 17/00* (2006.01)	*A61P 43/00* (2006.01)

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)

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)
Chemical Abstracts and Free Patents Online: structure search based on formula I

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0191378 A1 (CAMPBELL, M. ET AL) 16 August 2007 Page 12 - Example 4	1,7,13-15,22, 47,48
X	US 2008/0008660 A1 (RABENHORST, J. ET AL) 10 January 2008 Whole document – specifically selected compounds on pages 5-8 and 10	1,7,13-15,22

[X] Further documents are listed in the continuation of Box C [X] 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	Date of mailing of the international search report
4 August 2010	20 AUG 2010
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **MS CORRINA PARKER** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6222 3661

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/000745

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 6127392 A (LENNOX, J.R. ET AL) 3 October 2000 Abstract; columns 4-10; column 32, line 61; examples; claims	1,5,7,12, 13-15,21,22, 47,48
X	US 6646009 B2 (REDDY, E. P. ET AL) 11 November 2003 Table 4, compounds 12,16,17; table 5, compounds 35,37,38,41,43,45,47; columns 17-21; claim 55	1,7,13,17,18, 22,24,28, 30,32,33, 42,47,48
X	US 2007/0286892 A1 (HERZBERG, U. ET AL) 13 December 2007 Claim 3, lines 6-8	1,7,13,14,22
X	US 2007/0299101 A1 (COLLETTI, S.L. ET AL) 27 December 2007 Page 30, scheme 5; page 31-32, scheme 7; page 33, scheme 9; page 34, scheme 10; page 35-36, scheme 14; page 42, scheme 25	1,7,13,22
X	WO 2008/057862 A2 (BRISTOL-MYERS SQUIBB COMPANY) 15 May 2008 Page 101, examples 27 and 28	1,9,11,12,13, 14,22,26,29, 30,32
X	US 2002/0099089 A1 (HAUEL, N. ET AL) 25 July 2002 Whole Document – see as a small sample paragraphs 0243-0253, 0255, 0257-0259, 0262-0267, 0351, 0379-0385, 0415, 0431	1,7,11, 13-16,19-22, 26,30,32,33
X	US 6326510 B1 (BERNARDON, J) 4 December 2001 Examples 2, 13, 14, 26	1,7,9,11, 13-15,22,23, 28,29,30,32, 33
X	EP 0816329 A1 (HOECHST AKTIENGESELLSCHAFT) 7 January 1998 Compounds 165, 321, 322	1,7,9, 13-15,22,23, 28-30,32,33
X	US 2006/0014807 A1 (LIN, L.H.) 19 January 2006 Compounds B, E, N, U, Y, E', G', K', N', O', P', Z', E", G", J", K", M", P", T", X", Y", A"', D"', G"'-T"', V"', B"", C"", L"", P""-T"", V"", X"", Z"", D""	1-7, 12,13,17,22, 24,28,32,33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/000745

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 5663414 A (OINUMA, H. ET AL) 2 September 1997 Examples 1-26, 33-38, 40, 41, 47, 56-71, 77-83, 86, 89-92, 98	1,7,12,13,17, 18,22
X	US 5248825 A (DINERSTEIN, R.J. ET AL) 28 September 1993 Example 4	1,8,13
XP	US 7592373 B2 (LEHMANN-LINTZ, T. ET AL) 22 September 2009 Examples 3.1, 3.2	1,8,13
XP	WO 2009/082347 A1 (ASTRAZENECA AB) 2 July 2009 Examples 20,30-33,37-43,54,55,57,58,60,61,65,66,68,75,77,82-84,88-90,92-94,96,97,99-101,104,105,216,217,219-222,225,227a	1-7,13,17,18, 21,22,24,28, 30,32,33
XP	US 2009/0226537 A1 (SCHMAUS, G. ET AL) 10 September 2009 Pages 2-4, 20-23; claim 7	1,7,13-15,22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/000745

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.: **49**
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:

The claim does not comply with Rule 6.2(a) because it relies on references to the description and/or drawings.

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:

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 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2010/000745

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	2007191378	EP	1689699	WO	2005016867		
US	2008008660	CN	101198375	EP	1886662	EP	1893161
		JP	2007332143	KR	20070119545	US	2009297468
		WO	2006134013	WO	2006134120		
US	6127392	US	6046239				
US	6646009	CA	2439255	EP	1379508	US	2002165412
		WO	02067865				
US	2007286892	EP	2035008	US	2007287741	US	2009326035
		WO	2007146920				
US	2007299101	AU	2005305072	CA	2586156	CN	101056635
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		CA	2378382	CN	1414849	CO	5180639
		CZ	20020313	DE	19935219	EE	200200041
		EP	1261321	HR	20020072	HU	0204373
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		UY	26256	WO	0107020	ZA	200200694
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		FR	2759368	WO	9834909		
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US	2006014807	US	7671077	US	2009227790		
US	5663414	CA	2050591	EP	0468054	NO	913829
		US	5281626	US	5530118	WO	9112237
US	5248825	AU	84528/91	CA	2051501	CN	1059901
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		IE	913298	JP	7025812	NO	913683
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		EP	1708698	US	2005267093	UY	28689
		WO	2005063239				
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		US	2009163586	UY	31546		
US	2009226537	EP	1959915	WO	2007062957		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX