NOVEL TRIAZOLE AND OXAZOLE COMPOUNDS AS TRANSFORMING GROWTH FACTOR (TGF) INHIBITOR

Background of the Invention

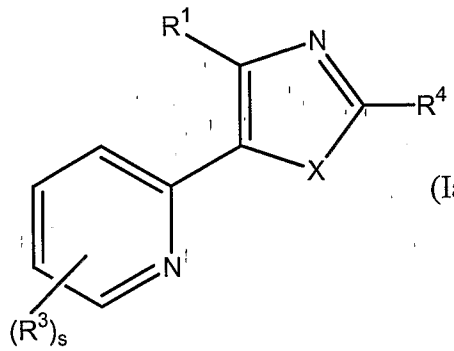
The present invention relates to novel oxazole and thiazole compounds, including derivatives thereof, to intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The compounds of the present invention are potent inhibitors of the transforming growth factor ("TGF")- β signaling pathway. They are useful in the treatment of TGF-β related disease states including, for example, cancer and fibrotic diseases.

TGF-β activates both antiproliferative and tumor-promoting signaling cascades. Three mammalian TGF-β isoforms have been identified (TGF-βI, -βII, and -βIII). TGF-β production promotes tumor progression while its blockade enhances antitumor activity. Blockade of TGF-β enhances antitumor immune responses and inhibits metastasis. Thus there exists a need in the art for compounds that inhibit the TGF-β signaling pathway. The present invention, as described below, answers such a need.

SUMMARY OF THE INVENTION

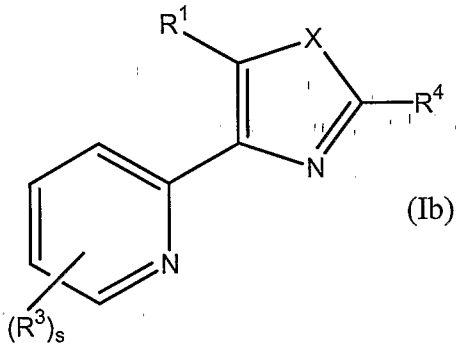
The present invention provides a novel compound containing a core oxazole or thiazole ring substituted with at least one substituted or unsubstituted 2-pyridyl moiety and at least one R^1 moiety as set forth herein, and all pharmaceutically acceptable salts, prodrugs, tautomers, hydrates, and solvates thereof. In a compound of the invention, the substituted or unsubstituted 2-pyridyl moiety and R^1 moiety can be in an 1,2-, 1,3- or 1,4- relationship around the core oxazole or thiazole ring; preferably, in an 1,2- or *ortho* relationship.

The present invention provides a compound of the formula (Ia) or (Ib):



(Ia)

, or



(Ib)

and all pharmaceutically acceptable salts, prodrugs, tautomers, hydrates, and solvates thereof, where X, R^1, R^3, R^4, and s are each as set forth below, with the proviso that when R^4 is a substituted phenyl moiety, then (a) R^1 is not naphthyl, phenyl or anthracenyl and (b) if R^1 is a phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to three heteroatoms independently selected from N, O and S, then the fused cyclic ring of said R^1 moiety is substituted; with the proviso that when R^4 is NH_2 and X is S, then R^1 is not an amino-substituted pyridyl or pyrimidinyl moiety; and

with the proviso that when in formula (Ia) R^4 is CH_3 and X is S, R^1 is not a 3,4-dimethoxy substituted phenyl moiety .

In another embodiment, the invention provides a compound of formulae (Ia)-(Ib), as set forth above, with the proviso that when R^4 is a substituted phenyl moiety, then (a) R^1 is not naphthyl, phenyl or anthracenyl and (b) if R^1 is a phenyl moiety fused with an aromatic or non-aromatic cyclic ring of 5-7 members containing up to three heteroatoms independently selected from N, O or S, then said phenyl moiety of R^1 contains at least one heteroatom selected from N, O, and S.

In another embodiment, the invention provides a compound of formulae (Ia)-(Ib), as set forth above, with the proviso that when R^4 is a substituted phenyl moiety, then (a) R^1 is not naphthyl, phenyl or anthracenyl and (b) if R^1 is a phenyl moiety fused with an aromatic or non-aromatic cyclic ring of 5-7 members containing up to three heteroatoms independently selected from N, O or S, then the fused cyclic ring of R^1 contains a C=O group and/or at least one substituted heteroatom.

In another embodiment, the invention provides a compound of formulae (Ia)-(Ib), as set forth above, with the proviso that when R^4 is a substituted phenyl moiety, then (a) R^1 is not naphthyl, phenyl or anthracenyl and (b) if R^1 is a phenyl moiety fused with an aromatic or non-aromatic cyclic ring of 5-7 members containing up to three heteroatoms independently selected from N, O or S, optionally substituted by =O, then the fused cyclic ring of R^1 further contains at least one substituted heteroatom.

In formulae (Ia)-(Ib), as set forth above:

X is O or S;

R^1 is a saturated, unsaturated, or aromatic C_3-C_{20} mono-, bi- or polycyclic ring optionally containing at least one heteroatom selected from the group consisting of N, O and S, wherein R^1 can optionally be further independently substituted with at least one moiety independently selected from the group consisting of, but not limited to, carbonyl, halo, halo(C_1-C_6)alkyl, perhalo(C_1-C_6)alkyl, perhalo(C_1-C_6)alkoxy,
(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, oxo, mercapto, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_5-C_{10})aryl or (C_5-C_{10})heteroaryl, (C_5-C_{10})aryloxy or (C_5-C_{10})heteroaryloxy, (C_5-C_{10})ar(C_1-C_6)alkyl or (C_5-C_{10})heteroar(C_1-C_6)alkyl, (C_5-C_{10})ar(C_1-C_6)alkoxy or (C_5-C_{10})heteroar(C_1-C_6)alkoxy, HO-(C=O)-, ester, amido, ether, amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_5-C_{10})heterocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkyl- and di(C_1-C_6)alkylamino, cyano, nitro, carbamoyl, (C_1-C_6)alkylcarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_5-C_{10})arylcarbonyl, (C_5-C_{10})aryloxycarbonyl,

(C_1-C_6)alkylsulfonyl, and (C_5-C_{10})arylsulfonyl; preferably, R^1 can optionally be further independently substituted with zero to two moieties independently selected from the group consisting of, but not limited to, halo(C_1-C_6)alkyl, perhalo(C_1-C_6)alkyl, perhalo(C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_5-C_{10})ar(C_1-C_6)alkoxy or (C_5-C_{10})heteroar(C_1-C_6)alkoxy, amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, and (C_5-C_{10})heterocyclyl(C_1-C_6)alkyl;

each R^3 is independently selected from the group consisting of: hydrogen, halo, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_5-C_{10})heteroaryl, (C_5-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_5-C_{10})heteroaryl-O-, (C_5-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, O_2N-, NC-, amino, $Ph(CH_2)_{1-6}HN$-, (C_1-C_6)alkyl HN-, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, amino(C=O)-, aminoO_2S-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[(((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_5-C_{10})heteroaryl-(C=O)-, (C_5-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_5-C_{10})heteroaryl-NH-(C=O)-, (C_5-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)- and (C_1-C_6)alkyl-(C=O)-O-; preferably, R^3 is hydrogen or (C_1-C_6)alkyl; more preferably, R^3 is hydrogen or methyl;

where alkyl, alkenyl, alkynyl, phenyl, heteroaryl, heterocyclic, cycloalkyl, alkoxy, phenoxy, amino of R^3 is optionally substituted by at least one substituent independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo, H_2N-, $Ph(CH_2)_{1-6}HN$-, and (C_1-C_6)alkylHN-;

s is an integer from one to five; preferably, one to two; more preferably, one;

R^4 is independently selected from the group consisting of: hydrogen, halo, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_5-C_{10})heteroaryl, (C_5-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_5-C_{10})heteroaryl-O-, (C_5-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, O_2N-, NC-, amino, $Ph(CH_2)_{1-6}HN$-, (C_1-C_6)alkylHN-, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, amino(C=O)-, aminoO_2S-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-((C_1-C_6)alkyl)-N-, phenyl-(C=O)-NH-, phenyl-(C=O)-((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_5-C_{10})heteroaryl-(C=O)-, (C_5-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, ((C_1-C_6)alkyl)$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-((C_1-C_6)alkyl)-N]-(C=O)-, (C_5-C_{10})heteroaryl-NH-(C=O)-, (C_5-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)- and (C_1-C_6)alkyl-(C=O)-O-; preferably, R^4 is hydrogen, (C_1-C_6)alkyl, or amino; more preferably, R^4 is hydrogen, methyl, or H_2N-;

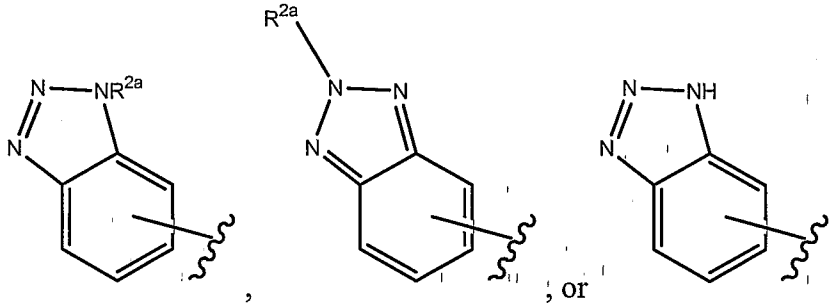
where alkyl, alkenyl, alkynyl, phenyl, heteroaryl, heterocyclic, cycloalkyl, alkoxy, phenoxy, amino of R^4 is optionally substituted by at least one substituent independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo, H_2N-, $Ph(CH_2)_{1-6}HN$-, (C_1-C_6)alkylHN-, (C_5-C_{10})heteroaryl and (C_5-C_{10})heterocyclyl;

with the proviso that when R^4 is a substituted phenyl moiety, then (a) R^1 is not naphthyl, phenyl or anthracenyl and (b) if R^1 is a phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to three heteroatoms independently selected from N, O and S, then the fused cyclic ring of said R^1 moiety is substituted;

with the proviso that when R^4 is NH_2 and X is S, then R^1 is not an amino-substituted pyridyl or pyrimidinyl moiety; and

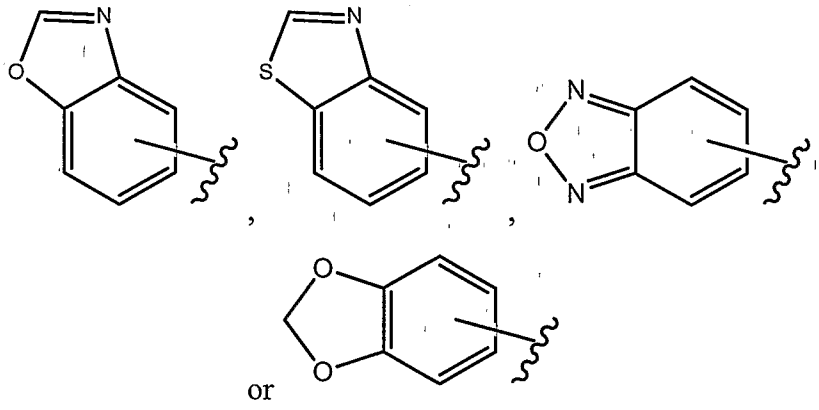
with the proviso that when in formula (Ia) R^4 is CH_3 and X is S, R^1 is not a 3,4-dimethoxy substituted phenyl moiety

In another embodiment of the invention, R^1 of formula (Ia) or (Ib), each as set forth above, is

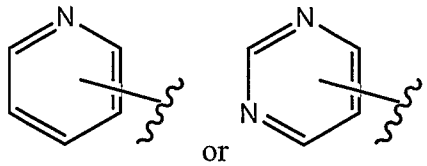


where R^{2a} is as set forth herein.

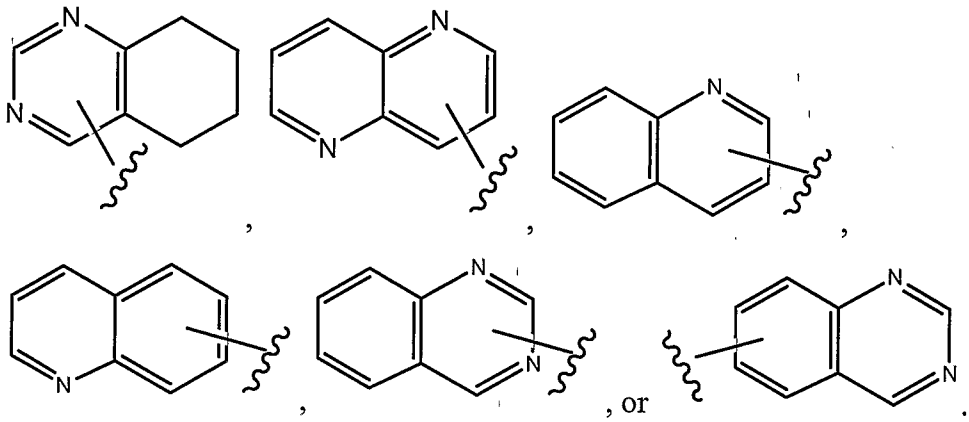
In another embodiment of the invention, R^1 of formula (Ia) or (Ib), each as set forth above, is



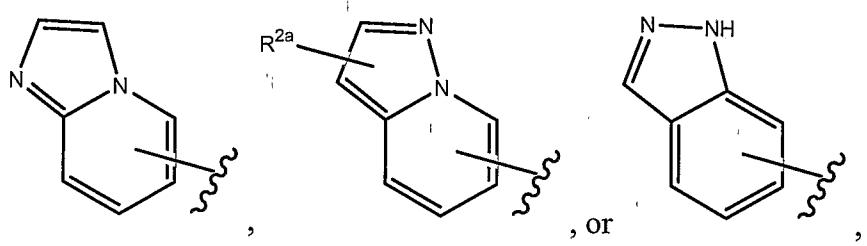
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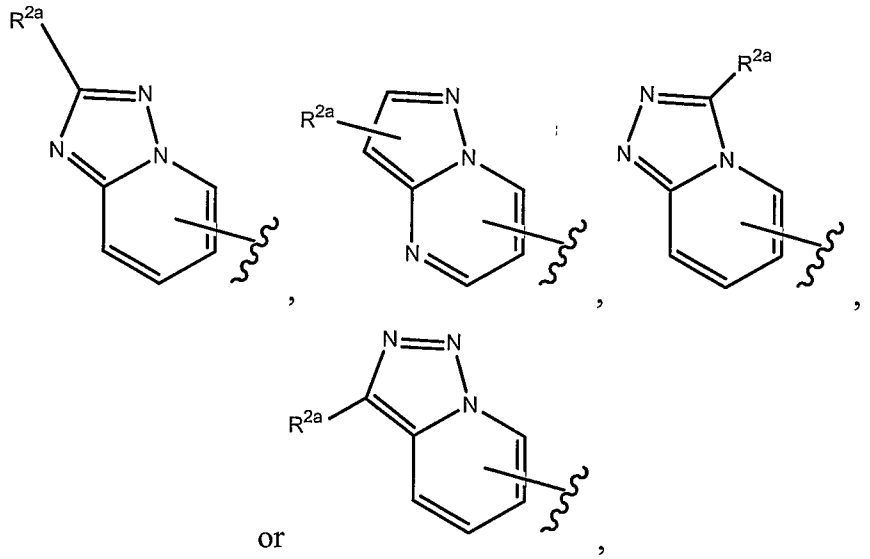


In another embodiment of the invention, R^1 of formula (Ia) or (Ib), each as set forth above, is



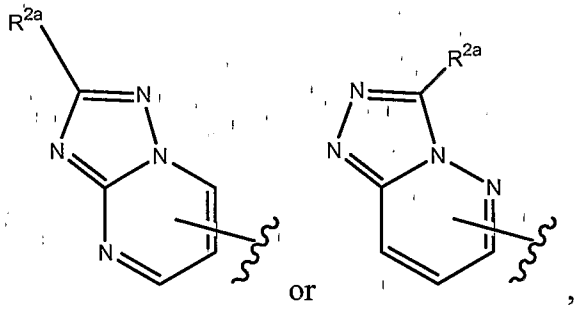
where R^{2a} is as set forth herein.

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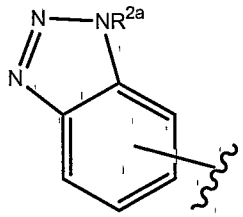
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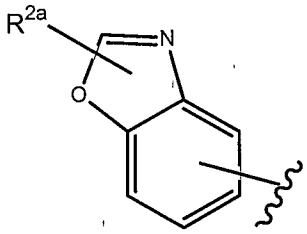
Each of R^1 above can optionally be further substituted by at least one R^{2a} group, as set forth herein.

In another embodiment of the invention, R^1 of formula (Ia), as set forth above, is

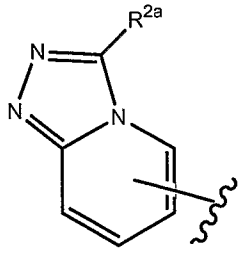


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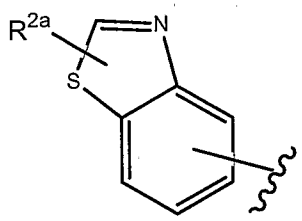
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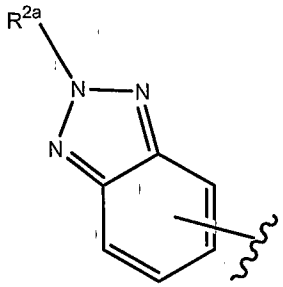
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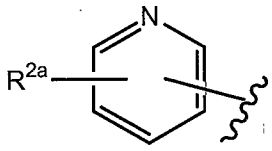


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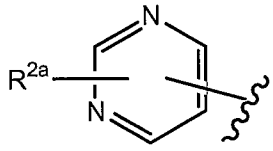


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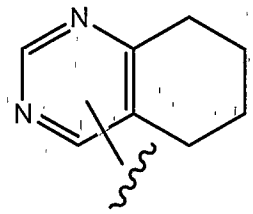
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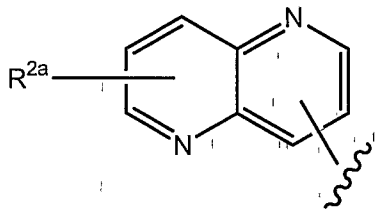
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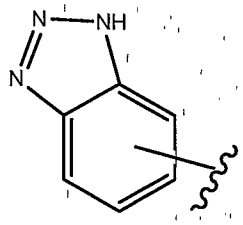
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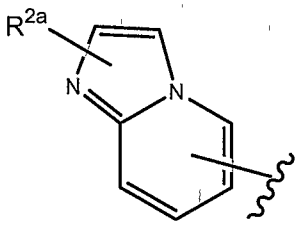
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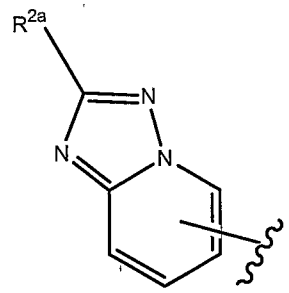
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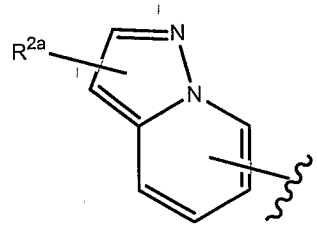


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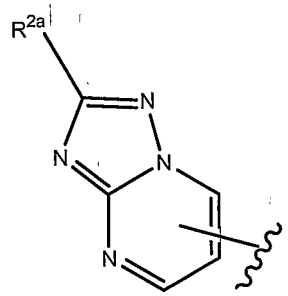
where R^{2a} is as set forth herein.

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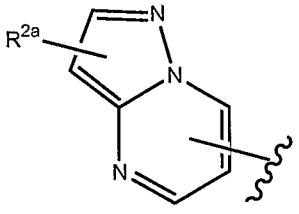
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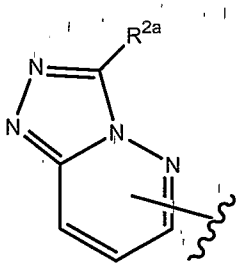
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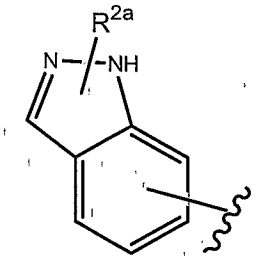
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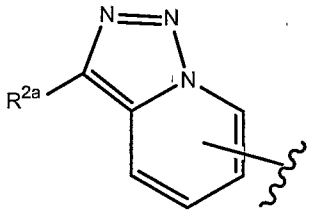


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In another embodiment of the invention, R^1 of formula (Ia), as set forth above, is

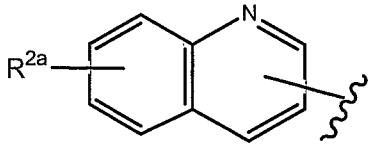


In another embodiment of the invention, R^1 of formula (Ia), as set forth above, is

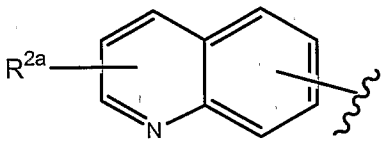


where R^{2a} is as set forth herein.

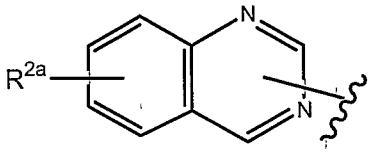
In another embodiment of the invention, R^1 of formula (Ia), as set forth above, is



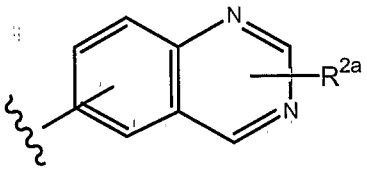
In another embodiment of the invention, R^1 of formula (Ia), as set forth above, is



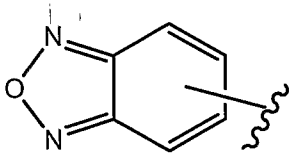
In another embodiment of the invention, R^1 of formula (Ia), as set forth above, is



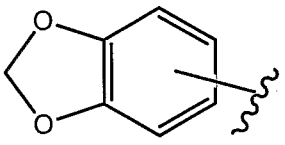
In another embodiment of the invention R^1 of formula (Ia), as set forth above, is



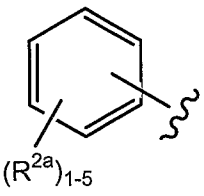
In another embodiment of the invention, R^1 of formula (Ia), as set forth above, is



In another embodiment of the invention, R^1 of formula (Ia), as set forth above, is

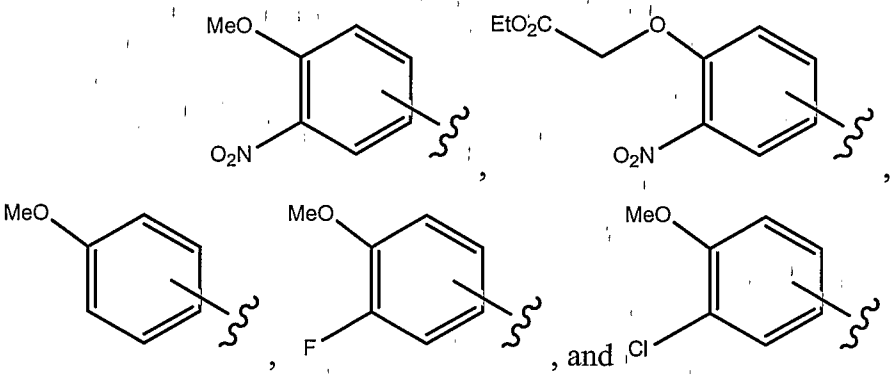


In another embodiment of the invention, R^1 of formulae (Ia)-(Ib), each as set forth above, is



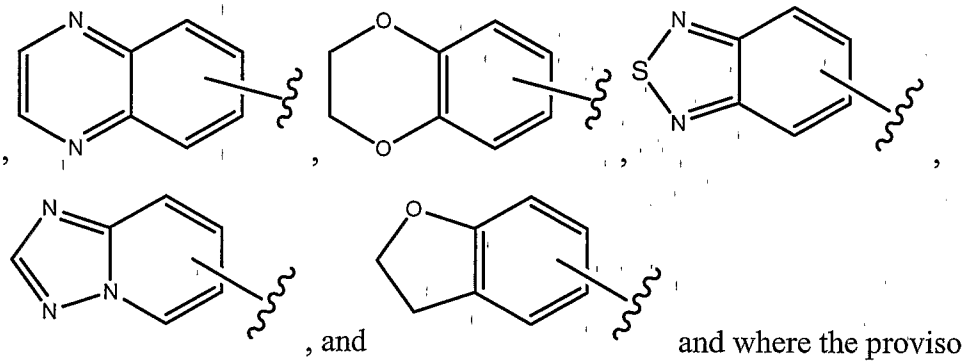
where R^{2a} is as set forth herein and where the proviso language does not apply.

In another embodiment of the invention, R^1 of formulae (Ia)-(Ib), each as set forth above, is selected from the group consisting of:



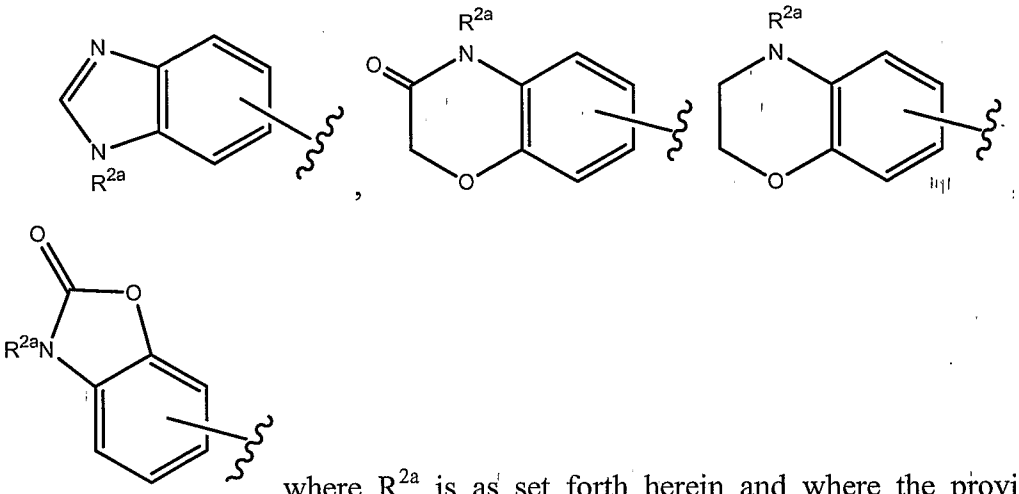
and where the proviso language does not apply.

In another embodiment of the invention, R^1 of formulae of (Ia)-(Ib), each as set forth above, is selected from the group consisting of:



and where the proviso language does not apply.

In another embodiment of the invention, R^1 of formulae of (Ia)-(Ib), each as set forth above, is selected from the group consisting of:



and where R^{2a} is as set forth herein and where the proviso language does not apply.

The invention also provides a pharmaceutical composition comprising at least one compound of the invention and a pharmaceutically acceptable carrier.

The invention further provides a method of preparation of a compound of the invention.

The invention still further provides a method of preventing or treating a TGF-related disease state in an animal or human comprising the step of administering a therapeutically effective amount of at least one compound of the invention to the animal or human suffering from the TGF-related disease state.

The invention still further provides the use of a compound in the preparation of a medicament for the prevention or treatment of a TGF-related disease state in an animal or human.

DEFINITIONS

As used herein, the article "a" or "an" refers to both the singular and plural form of the object to which it refers.

As used herein, the term "alkyl," as well as the alkyl moieties of other groups referred to herein (*e.g.*, alkoxy) refers to a linear or branched saturated hydrocarbon (*e.g.*, methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl).

As used herein, the term "cycloalkyl" refers to a mono or bicyclic carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl,

cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl).

As used herein, the term "halogen" or "halo" refers to fluoro, chloro, bromo or iodo or fluoride, chloride, bromide or iodide.

As used herein, the term "halo-substituted alkyl" or "haloalkyl" refers to an alkyl radical, as set forth above, substituted with one or more halogens, as set forth above, including, but not limited to, chloromethyl, dichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and 2,2,2-trichloroethyl.

As used herein, the term "perhaloalkyl" refers to an alkyl radical, as set forth above, where each hyrdrogen of the alkyl group is replaced with a "halogen" or "halo", a set forth above.

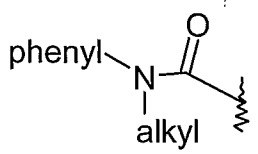
As used herein, the term "alkenyl" refers to a linear or branched hydrocarbon chain radical containing at least two carbon atoms and at least one double bond. Examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl.

As used herein, the term "alkynyl" refers to a linear or branched hydrocarbon chain radical having at least one triple bond including, but not limited to, ethynyl, propynyl, and butynyl.

As used herein, the term "carbonyl" refers to a >C=O moiety.

Alkoxycarbonylamino (*i.e.* alkoxy(C=O)-NH-) refers to an alkyl carbamate group. The carbonyl group is also equivalently defined herein as (C=O).

As used herein, the term "phenyl-[(alkyl)-N]-(C=O)- " refers to a N.N'-disubstituted amide group of the formula



As used herein, the term "aryl" refers to an aromatic radical such as, for example, phenyl, naphthyl, tetrahydronaphthyl, and indanyl.

As used herein, the term "heteroaryl" refers to an aromatic group containing at least one heteroatom selected from O, S and N. For example, heteroaryl groups include, but are not limited to, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl,

furyl, imidazolyl, pyrrolyl, oxazolyl (*e.g.*, 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (*e.g.*, 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (*e.g.*, 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (*e.g.*, 1,2,3-oxadiazolyl), thiadiazolyl (*e.g.*, 1,3,4-thiadiazolyl), quinolyl, isoquinolyl, benzothienyl, benzofuryl, and indolyl.

As used herein, the term "heterocyclic" refers to a saturated or unsaturated C_3-C_{20} mono-, bi- or polycyclic group containing at least one heteroatom selected from N, O, and S. Examples of heterocyclic groups include, but are not limited to, azetidinyl, tetrahydrofuranyl, imidazolidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, thiomorpholinyl, tetrahydrothiazinyl, tetrahydro-thiadiazinyl, morpholinyl, oxetanyl, tetrahydrodiazinyl, oxazinyl, oxcithiazinyl, indolinyl, isoindolinyl, quincuclidinyl, chromanyl, isochromanyl, benzocazinyl, and the like. Examples of monocyclic saturated or unsaturated ring systems are tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 1,3-oxazolidin-3-yl, isothiazolidine, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, thiomorpholin-yl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazin-yl, morpholin-yl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-oxazin-2-yl, and 1,2,5-oxathiazin-4-yl.

As used herein, the term "pharmaceutically acceptable acid addition salt" refers to non-toxic acid addition salts, *i.e.*, salts derived from pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

As used herein, the term "pharmaceutically acceptable base addition salt" refers to non-toxic base addition salts, *i.e.*, salts derived from such pharmacologically acceptable cations such as alkali metal cations (*e.g.*, potassium and sodium) and alkaline earth metal cations (*e.g.*, calcium and magnesium), ammonium or water-

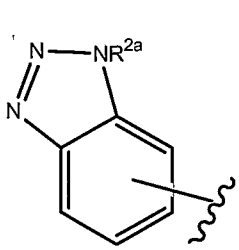
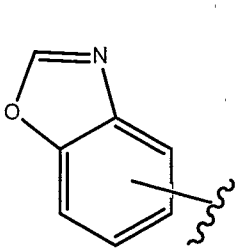
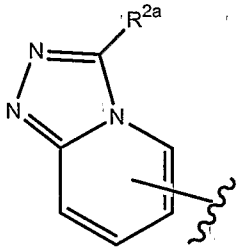
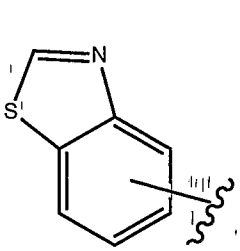
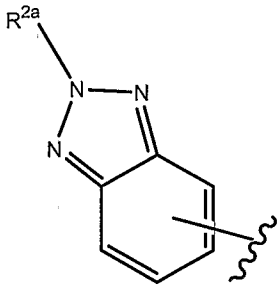
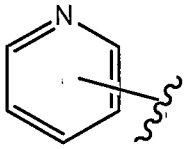
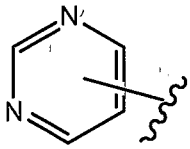
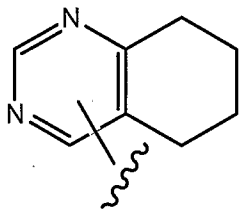
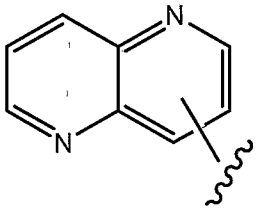
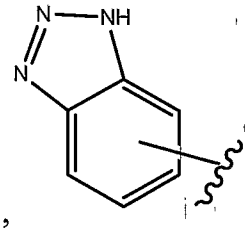
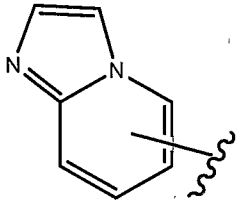
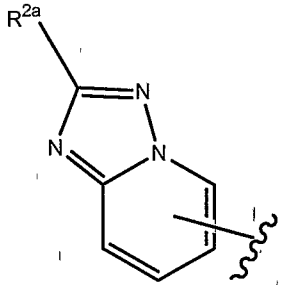
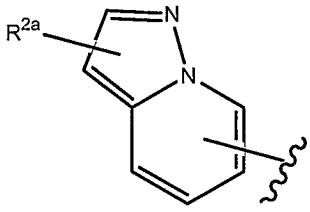
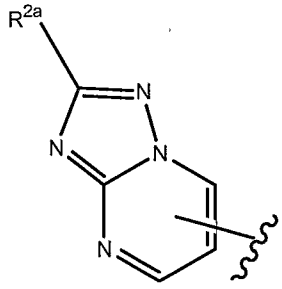
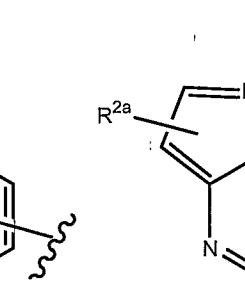
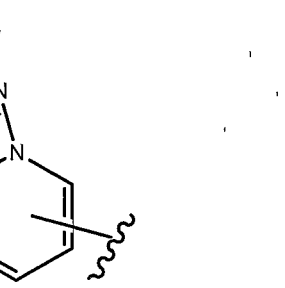
soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

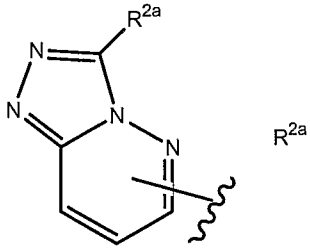
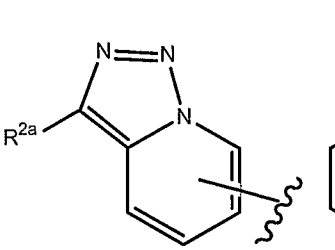
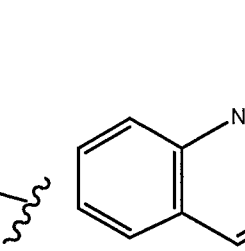
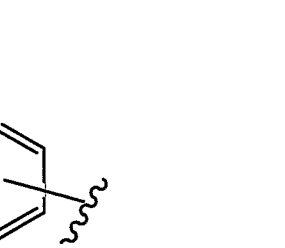
As used herein, the term "suitable substituent", "substituent" or "substituted" refers to a chemically and pharmaceutically acceptable functional group, *i.e.*, a moiety that does not negate the inhibitory and/or therapeutic activity of the inventive compounds. Such suitable substituents may be routinely selected by those skilled in the art. Illustrative examples of suitable substituents include, but are not limited to, carbonyl, halo, haloalkyl, perfluoroalkyl, perfluoroalkoxy, alkyl, alkenyl, alkynyl, hydroxy, oxo, mercapto, alkylthio, alkoxy, aryl or heteroaryl, aryloxy or heteroaryloxy, aralkyl or heteroaralkyl, aralkoxy or heteroaralkoxy, HO-(C=O)-, ester, amido, ether, amino, alkyl- and dialkylamino, cyano, nitro, carbamoyl, alkylcarbonyl, alkoxycarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylcarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl and the like. Those skilled in the art will appreciate that many substituents can be substituted by additional substituents.

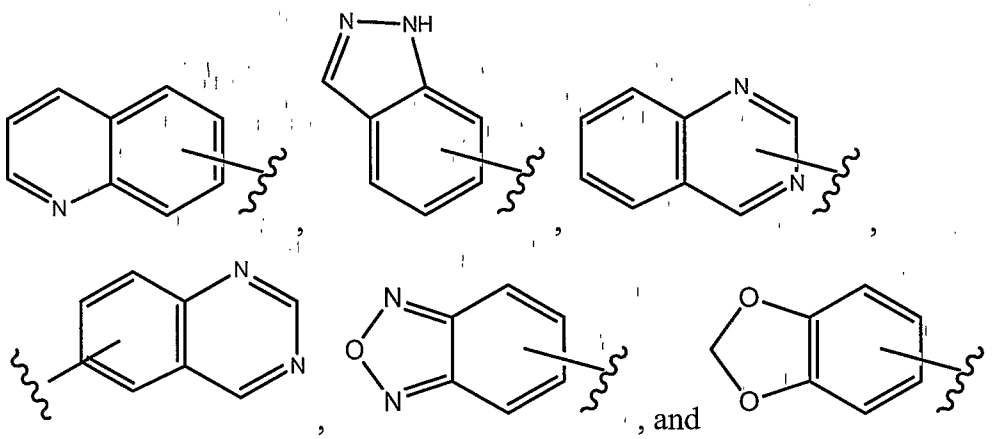
As used herein, the term "TGF-related disease state" refers to any disease state mediated by the production of TGF-ß.

As used herein, the term "Ph" refers to phenyl.

As used herein, the term "a saturated, unsaturated, or aromatic C_3-C_{20} mono-, bi- or polycyclic ring optionally containing at least one heteroatom" refers to, but is not limited to,



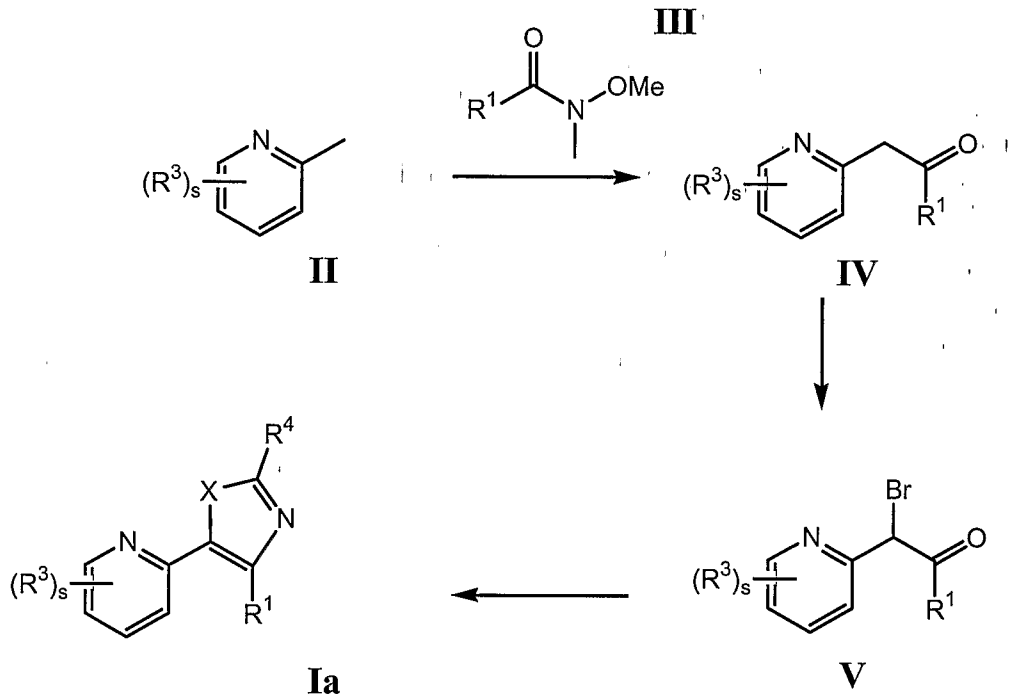
where R^{2a} is independently selected from the group consisting of: $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_5\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkylaryl, amino, carbonyl, carboxyl, $(C_2\text{-}C_6)$acid, $(C_1\text{-}C_6)$ester, $(C_5\text{-}C_{10})$heteroaryl, $(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_6)$alkoxy, nitro, halo, hydroxyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$ester, and those groups described in U.S. Application Nos. 10/094,717, 10/094,760, and 10/115,952, each of which is herein incorporated in its entirety by reference; and where alkyl, alkenyl, alkynyl, cycloalkyl, aryl, amino, acid, ester, heteroaryl, heterocyclyl, and alkoxy of R^{2a} is optionally substituted by at least one moiety independently selected from the group consisting of halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, perhalo$(C_1\text{-}C_6)$alkyl, phenyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_5\text{-}C_{10})$heteroaryl, $(C_5\text{-}C_{10})$heterocyclic, formyl, NC-, $(C_1\text{-}C_6)$alkyl-(C=O)-, phenyl-(C=O)-, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $((C_1\text{-}C_6)\text{alkyl})_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, O_2N-, amino, $(C_1\text{-}C_6)$alkylamino, $((C_1\text{-}C_6)\text{alkyl})_2$-amino, $(C_1\text{-}C_6)$alkyl-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, H_2N-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-NH-, $((C_1\text{-}C_6)\text{alkyl})_2$N-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-[$(C_1\text{-}C_6)$alkyl)-N]-, $((C_1\text{-}C_6)\text{alkyl})_2$N-(C=O)-[$(C_1\text{-}C_6)$alkyl-N]-, phenyl-HN-(C=O)-NH-, $(\text{phenyl})_2$N-(C=O)-NH-, phenyl-HN-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, $(\text{phenyl-})_2$N-(C=O)-[$(C_1\text{-}C_6)$alkyl)-N]-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-[$(C_1\text{-}C_6)$alkyl)-N]-, phenyl-O-(C=O)-NH-, phenyl-O-(C=O)-[(alkyl)-N]-, $(C_1\text{-}C_6)$alkyl-SO_2NH-, phenyl-SO_2NH-,

$(C_1\text{-}C_6)$alkyl-SO_2-, phenyl-SO_2-, hydroxy, $(C_1\text{-}C_6)$alkoxy, perhalo$(C_1\text{-}C_6)$alkoxy, phenoxy, $(C_1\text{-}C_6)$alkyl-(C=O)-O-, $(C_1\text{-}C_6)$ester-$(C_1\text{-}C_6)$alkyl-O-, phenyl-(C=O)-O-, H_2N-(C=O)-O-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-O-, $((C_1\text{-}C_6)\text{alkyl})_2$N-(C=O)-O-, phenyl-HN-(C=O)-O-, and $(\text{phenyl})_2$N-(C=O)-O-.

DETAILED DESCRIPTION OF THE INVENTION

The following reaction schemes illustrate the preparation of the compounds of the present invention. A compound of the invention may be prepared by methods analogous to those described in U.S. Application Nos. 10/094,717, 10/094,760, and 10/115,952 and WO 02/40476. Unless otherwise indicated, R^1, R^3, R^4, R^{2a}, X and s in the reaction schemes and the discussion that follow are defined above.

SCHEME 1



Scheme 1 refers to the preparation of compounds of the formula Ia. Referring to Scheme 1, a compound of the formula IV was prepared from a compound of the formula II by treating with a base, such as butyl lithium, at a temperature of about

-60°C for a time period of about 90 minutes, followed by the slow addition of an amide of the formula III, which is either commercially available or prepared according to Preparation C, as set forth below, in a polar aprotic solvent, such as tetrahydrofuran. The aforesaid reaction was run at a temperature from about -78°C to about 0°C, preferably about -20°C, for a period from about 1 hour to about 10 hours, preferably about 3 hours. A compound of formula II is commercially available.

Alternatively the compound of formula IV is prepared according to the methods of Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J.; J. Org. Chem., Vol. 65, pp. 8415-8420 (2000).

The compound of formula V was prepared from a compound of the formula IV by reaction with Br_2 in a polar solvent. Suitable solvents included acetic acid, chloroform or methylene chloride, preferably acetic acid. The aforesaid reaction was conducted at a temperature of about 0°C to about 30°C, preferably at about 22°C (room temperature) for a period from about 10 minutes to about 4 hours, preferably about 30 minutes.

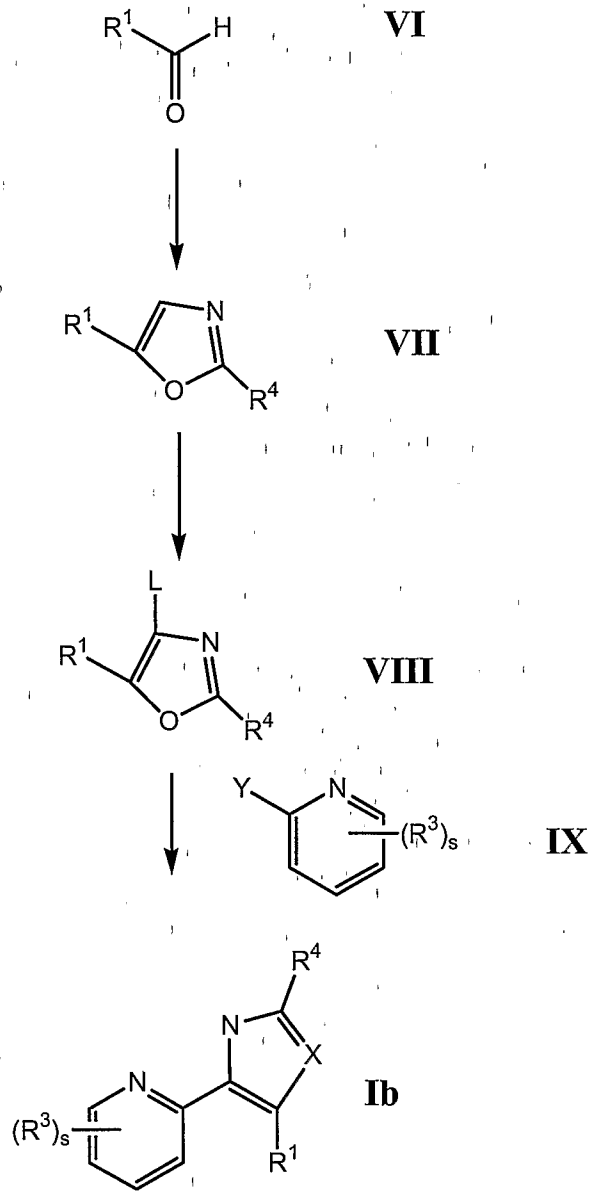
The compound of the formula Ia was prepared from a compound of the formula V, wherein X is oxygen, by first treating V with a carboxylate salt such as potassium acetate in a polar solvent such as N,N'-dimethylformamide, tetrahydrofuran, or methylene chloride, preferably N,N'-dimethylformamide. The aforesaid reaction was conducted at a temperature of about 50°C to about 100°C, preferably at about 60°C for a period from about 10 minutes to about 4 hours, preferably about one hour. The resulting acetate adduct was then treated with ammonium acetate in a polar protic solvent such as acetic acid, ethanol or tert-butyl alcohol, preferably acetic acid. The aforesaid reaction was conducted at a temperature of about 80°C to about 120°C, preferably at about 105°C for a period from about 1 hour to about 4 hours, preferably about 3 hours.

The compound of the formula Ia was prepared from a compound of the formula V, wherein X is sulfur, by treating V with a thioamide derivative such as thiourea in the presence of a base, such as potassium carbonate, in a polar protic

solvent such as methanol, ethanol, or iso-propanol, preferably ethanol. The aforesaid reaction was conducted at a temperature of about 50°C to about 100°C, preferably at about 80°C for a period from about 5 hours to about 18 hours, preferably about 12 hours.

Alternatively, compounds of the invention can be prepared from compounds of formula V according to methods described in the literature (Gauthier, J. Y.; Leblanc, Y.; Black, C.; Chan, C.-C.; Cromlish, W. A.; Gordon, R.; Kennedey, B. P.; Lau, C. K.; Léger, S.; Wang, Z.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. Bioorg. Med. Chem. Lett. 1996, 6, 87-92).

SCHEME 2



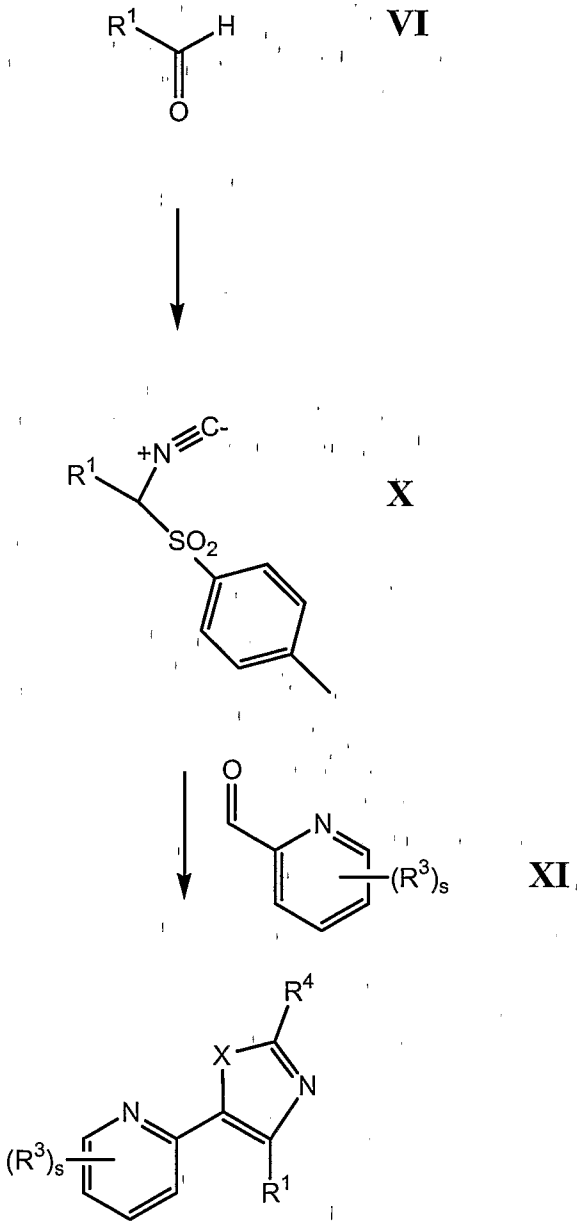
Scheme 2 refers to the preparation of compounds of the formula Ib. In Scheme 2, L is a halogen, such as bromine or chlorine. Referring to Scheme 2, a compound of the formula VII was prepared from a compound of the formula VI, which is either commercially available or can be prepared according to the procedure described in Preparation A, as set forth below, by treatment with 1-isocyanomethanesulfonyl-4-methyl-benzene in the presence of base, such as potassium carbonate, in a polar protic solvent such as methanol, ethanol, or iso-propanol, preferably methanol. The

aforesaid reaction was conducted at a temperature of about 50°C to about 100°C, preferably at about 70°C for a period from about 1 hour to about 5 hours, preferably about 3 hours. (Sisko, J.; Kassik, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A.; J. Org. Chem. 2000, 65, 1516-1524).

A compound of the formula VIII, wherein L is bromine, was prepared from a compound of the formula VII by first treatment with a strong base, such as lithium bis(trimethylsilyl)amide, in a polar solvent such as N,N'-dimethylformamide, tetrahydrofuran or diethyl ether, preferably N,N'-dimethylformamide. The aforesaid reaction was conducted at a temperature of about -90°C to about -50°C, preferably at about -78°C for a period from about 30 minutes to about 2 hours, preferably about 1 hour. The resulting solution was then treated with a source of bromine, such as N-bromosuccinamide, at a temperature of about -90°C to about -50°C, preferably at about -78°C for a period from about 30 minutes to about 2 hours, preferably about 1 hour.

A compound of the formula Ib may be prepared from a compound of the formula VIII by treatment with a compound of the formula IX, wherein Y is zinc bromide, in the presence of a palladium (0) catalyst, such as tetrakis(triphenylphosphine)palladium(0), in a polar aprotic solvent, such as tetrahydrofuran. The aforesaid reaction was conducted at a temperature of about 50°C to about 100°C, preferably at about 70°C for a period from about 5 hours to about 18 hours, preferably about 12 hours.

SCHEME 3

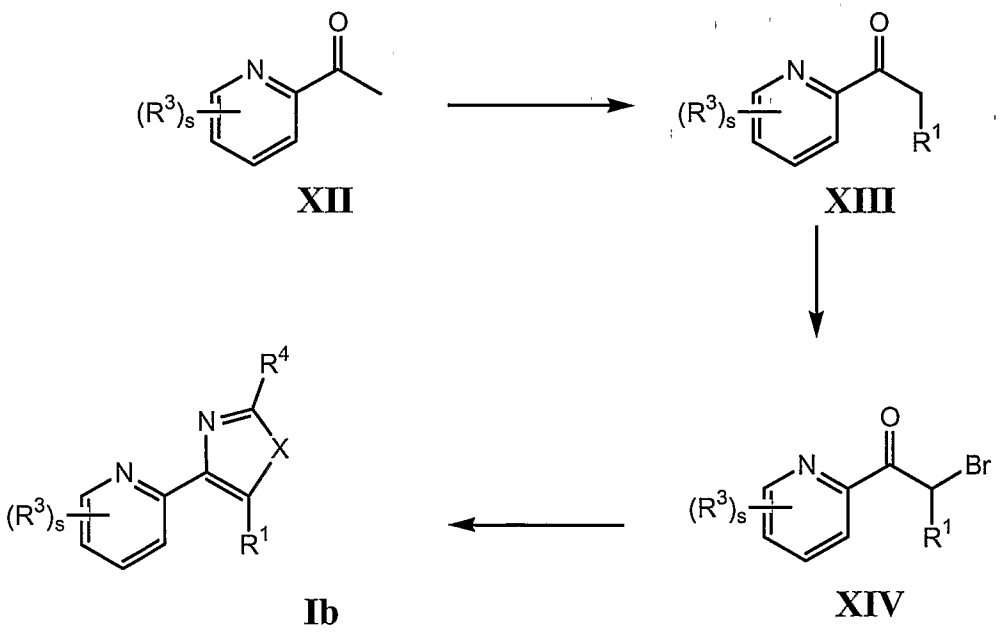


Scheme 3 refers to the preparation of compounds of the formula Ia. Referring to Scheme 3, a compound of the formula X was prepared from a compound of the formula VI, which is either commercially available or can be prepared according to the procedure described in Preparation A, as set forth below, by first treatment with 4-methyl-benzenesulfinic acid and an acid, such as 10-camphorsulfonic acid, in formamide. The aforesaid reaction was conducted at a temperature of about 50°C to about 100°C, preferably at about 75°C for a period

from about 1 hour to about 7 hours, preferably about 4 hours. The resulting product was then treated with a dehydrating agent, such as phosphorous oxychloride in a polar aprotic solvent such as tetrahydrofuran, chloroform or methylene chloride, preferably tetrahydrofuran. The aforesaid reaction was conducted at a temperature of about 0°C to about 30°C, preferably at about 22°C (ambient temperature) for a period from about 24 hours to about 52 hours, preferably about 48 hours.

A compound of the formula Ia may be prepared from a compound of the formula X by treatment with an aldehyde of the formula XI, which is either commercially available or may be prepared according to Preparation E, as set forth below, in the presence of a base, such as potassium carbonate, in a polar protic solvent such as methanol, ethanol or iso-propanol, preferably methanol. The aforesaid reaction was conducted at a temperature of about 50°C to about 100°C, preferably at about 70°C for a period from about 1 hour to about 5 hours, preferably about 2 hours. (Sisko, J.; Kassik, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A.; J. Org. Chem. 2000, 65, 1516-1524).

SCHEME 4



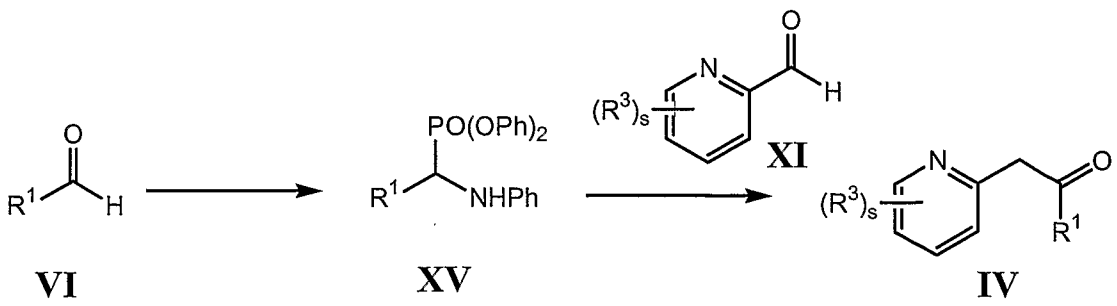
Scheme 4 refers to the preparation of compounds of the formula Ib. Referring to Scheme 4, a compound of the formula XIII was prepared from compound of the formula XII, which is either commercially available or prepared according to Preparation B, as set forth below, by reaction with an heteroaryl chloride of the formula R^1-Cl, in the presence of a catalyst such as palladium II acetate, a base, such as potassium tert-butoxide, and AMPHOS® (*i.e.*, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl, commercially available from Strem Chemicals, Newburyport, MA) in a polar aprotic solvent such as tetrahydrofuran. The aforesaid reaction was run at a temperature from about 50°C to about 100°C, preferably about 75°C, for a period from about 6 hours to about 24 hours, preferably about 18 hours.

The compound of formula XIV was prepared from a compound of the formula XIII according to the procedure described in Scheme 1 for the preparation of a compound of the formula IV from a compound of the formula III.

The compound of formula Ib was prepared from a compound of the formula XIV according to the procedure described in Scheme 1 for the preparation of a compound of the formula Ia from a compound of the formula V.

Alternatively, compounds of the invention can be prepared from compounds of formula XIV according to methods described in the literature (Gauthier, J. Y.; Leblanc, Y.; Black, C.; Chan, C.-C.; Cromlish, W. A.; Gordon, R.; Kennedey, B. P.; Lau, C. K.; Léger, S.; Wang, Z.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. Bioorg. Med. Chem. Lett. 1996, 6, 87-92).

SCHEME 5



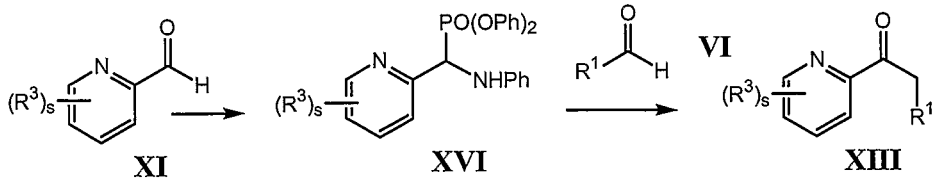
VI **XV** **IV**

Scheme 5 refers to the preparation of compounds of the formula IV, which are intermediates useful in the preparation of compounds of the formula Ia in Scheme 1. Referring to Scheme 5, compounds of the formula XV were prepared from aldehydes of the formula VI by first treatment with an aromatic amine, such as aniline, in a polar solvent. Suitable solvents include ethyl acetate, isopropyl acetate, or tetrahydrofuran, preferably isopropyl acetate. The resulting reaction mixture is heated to a temperature from about 50°C to about 100°C, preferably about 60°C, and then slowly treated with phosphorous acid diphenyl ester. The temperature of the reaction mixture was maintained for a period from about 30 minutes to about 3 hours, preferably about 1 hour and then cooled to ambient temperature overnight.

A compound of the formula IV was prepared from a compound of the formula XV by reaction with a pyridine aldehyde of the formula XI in the presence of a base, such as potassium tert-butoxide, in a polar solvent. Suitable solvents include ethyl acetate, isopropyl acetate, or tetrahydrofuran, preferably a mixture of tetrahydrofuran and isopropyl acetate. The aforesaid reaction was run at a temperature from about 0°C to about 100°C, preferably about 22°C (ambient temperature), for a period from about 30 minutes to about 5 hours, preferably about 2 hours. The resulting reaction mixture was then treated with acid, such as hydrochloric acid for a period from about 30 minutes to about 5 hours, preferably about 1 hour.

Alternatively the compound of formula VI is prepared according to the methods of Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J.; J. Org. Chem., Vol. 65, pp. 8415-8420 (2000).

SCHEME 6



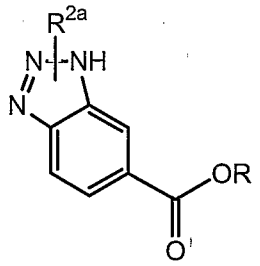
Scheme 6 refers to the preparation of compounds of the formula XIII, which are intermediates useful in the preparation of compounds of the formula Ib in

Scheme 4. Referring to Scheme 6, compounds of the formula XVI were prepared from pyridine aldehydes of the formula XI according to the procedure described in Scheme 5 for the preparation of a compound of the formula XV from a compound of the formula VI.

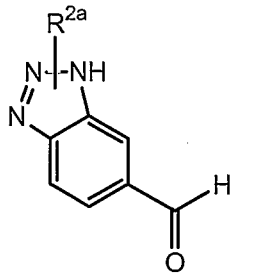
A compound of the formula XIII was prepared from a compound of the formula XVI according to the procedure described in Scheme 5 for the preparation of a compound of the formula IV from a compound of the formula XV.

Alternatively the compound of formula XIII is prepared according to the methods of Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J.; J. Org. Chem., Vol. 65, pp. 8415-8420 (2000).

SCHEME 7



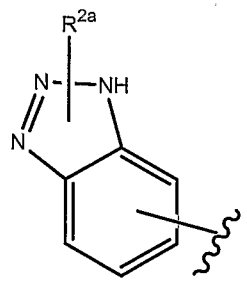
XVIII



VI

(Ia)-(Ib)

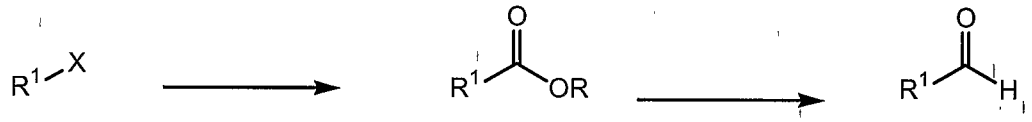
Scheme 7 refers to the preparation of compounds of the formula Ia and Ib where R^1 is



Referring to Scheme 7, compounds of the formula VI were prepared from compounds of the formula XVIII, which are either commercially available or can be prepared according to the procedure described in Preparation A, as set forth below.

In Scheme 7 the compounds Ia and Ib may be prepared from compound VI according to procedures described in Schemes 1, 2, 3, 5, and 6.

PREPARATION A



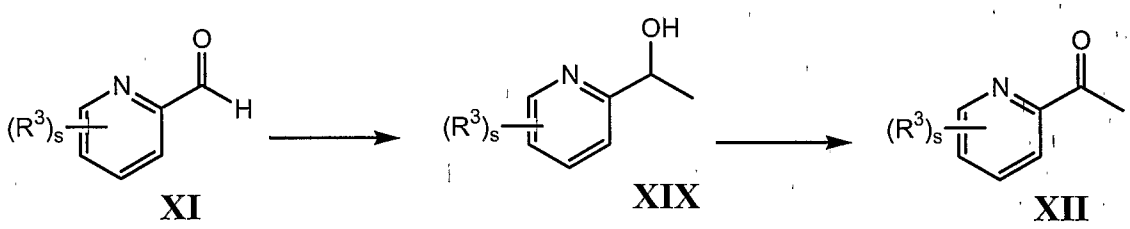
XVII **XVIII** **VI**

Preparation A refers to the preparation of compounds of the formula VI, which are intermediates useful in the preparation of compounds of the formula Ib, IV and XIII in Scheme 2, Scheme 3, Scheme 5 and Scheme 6. In Preparation A, R is a simple alkyl group such as methyl or ethyl. Referring to Preparation A, compounds of the formula XVIII were prepared from a compound of the formula XVII, wherein X is a chloride or bromide, by an alkoxycarbonylation reaction. Suitable conditions include metal-halogen exchange with butyl lithium in a solvent such as tetrahydrofuran at a temperature of about 0°C, for a period of time of about 30 minutes, followed by the addition of ethylchloroformate at a temperature of about 0°C, followed by a period of time of about 2.4 hours at about 50°C.

The compound of the formula VI was prepared from a compound of the formula XVIII with a two-step process. First the compound of formula XVIII was treated with a reducing agent. Suitable reducing agents include lithium borohydride,

sodium borohydride, lithium aluminum hydride, and borane in tetrahydrofuran. Suitable solvents include methanol, ethanol, tetrahydrofuran, diethyl ether, and dioxane. The aforesaid reaction was run at a temperature from about 0°C to about 100°C, preferably about 65°C, for a period from about 10 minutes to about 1 hour, preferably about 30 minutes. The resulting primary alcohol was then oxidized to the corresponding aldehyde of the formula VI by treating with an oxidizing agent, such as N-methyl morpholine N-oxide/TPAP, Dess-Martin reagent, PCC or oxalyl chloride-DMSO, preferably oxalyl chloride-DMSO. Suitable solvents for the aforesaid reaction include chloroform, tetrahydrofuran, or dichloromethane. The aforesaid reaction was conducted at a temperature from about -78°C to about 22°C for a time from about 15 minutes to about 3 hours, preferably about 1 hour.

PREPARATION B



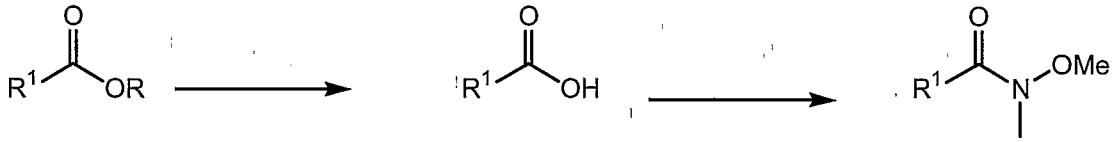
XI **XIX** **XII**

Preparation B refers to the preparation of compounds of the formula XII, which are intermediates useful in the preparation of compounds of the formula Ib in Scheme 4. Referring to Preparation B, a compound of formula XIX was prepared from a compound of the formula XI by reaction with methyl magnesium bromide in a polar solvent such as a mixture of tetrahydrofuran and toluene. The aforesaid reaction was run at a temperature from about -78°C to about 0°C, preferably about -60°C, for a period from about 10 minutes to about 1 hour, preferably about 40 minutes, followed by a period of about 90 minutes at a temperature of about -10°C.

The compound of formula XII was prepared from a compound of the formula XIX by treating with an oxidizing agent, such as N-methyl morpholine N-oxide/TPAP, Dess-Martin reagent, PCC or oxalyl chloride-DMSO, preferably oxalyl chloride-DMSO. Suitable solvents for the aforesaid reaction include chloroform, tetrahydrofuran, or dichloromethane. The aforesaid reaction was conducted at a

temperature from about -78°C to about 22°C for a time from about 15 minutes to about 3 hours, preferably about 1 hour.

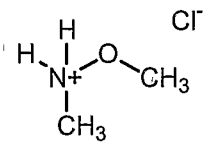
PREPARATION C



XVIII **XX** **III**

Preparation C refers to the preparation of compounds of the formula III, which are intermediates useful in the preparation of compounds of the formula Ia in Scheme 1. In Preparation C, R is a simple alkyl group such as methyl or ethyl. Referring to Preparation C, compounds of the formula XX were prepared from a compound of the formula XVIII, which may be prepared according to a procedure described in Preparation A or are commercially available, by treatment with a base such as lithium hydroxide, in a polar protic solvent. Suitable solvents for the aforesaid reaction included methanol, ethanol, and water. The aforesaid reaction was conducted at a temperature from about 0°C to about 30°C preferably about 22°C (room temperature) for a time from about 15 minutes to about 3 hours, preferably about 1 hour.

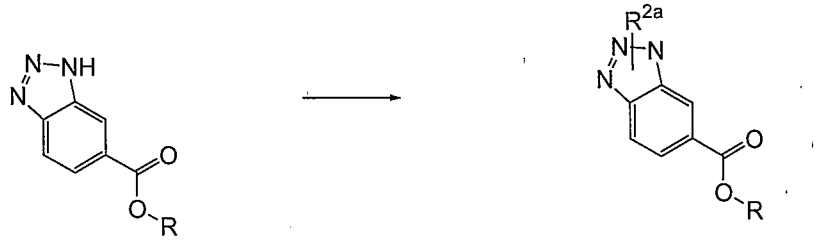
The compound of the formula III was prepared from a compound of the formula XX by reaction with a suitable activating agent and a compound of the formula



and a base. Suitable activating agents included thionyl chloride, carbonyldiimidazole, EDCI and DCC, preferably oxalyl chloride. Suitable bases included triethylamine, Hunig's base, or DBU, preferably triethylamine. Suitable solvents for the aforesaid reaction include methylene chloride, N,N'-dimethylformamide, tetrahydrofuran, and a mixture thereof, preferably methylene chloride. The aforesaid reaction was conducted at a temperature from about 0°C to

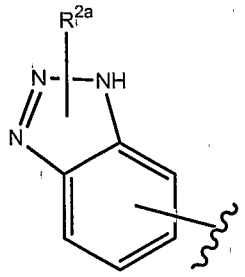
about 30°C, preferably about 22°C (room temperature) for a time from about 6 hours to about 48 hours, preferably about 12 hours.

PREPARATION D



XXI XVIII

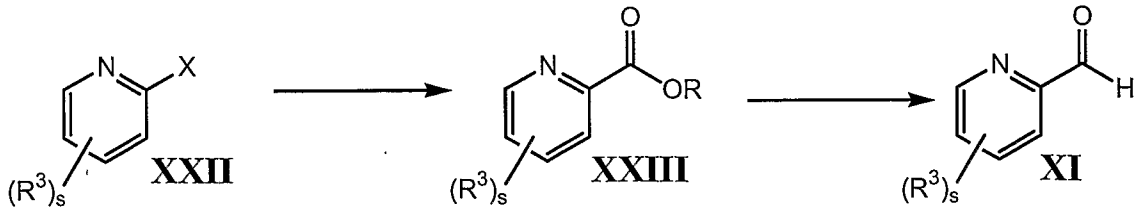
Preparation D refers to the preparation of compounds of the formula XVIII, which is an intermediate useful in the preparation of compounds of formula (Ia) and (Ib), each as set forth above, where R^1 is



In Preparation D, R is (C_1-C_6)alkyl. The compound of formula XVIII was prepared from a compound of formula XXI by treatment with an alkyl halide, such as methyl iodide, in the presence of a base such as sodium hydride, in a polar aprotic solvent such as N,N'-dimethylformamide.

Compounds of the formula XXI are commercially available or can be made by methods well known to those of ordinary skill in the art.

PREPARATION E



XXII XXIII XI

Preparation E refers to the preparation of compounds of the formula XI, which are intermediates useful in the preparation of compounds of formula (Ia) and (Ib), each as set forth above. In Preparation E, R is a simple alkyl group such as methyl or ethyl. Referring to Preparation E, compounds of the formula XXIII were prepared from heteroarylhalides of the formula, XXII, wherein X is a chloride or bromide, according to the procedure described for the preparation of compound XVIII from compound XVII in Preparation A.

The compound of the formula XI was prepared from a compound of the formula XXIII according to the two-step process described for the preparation of compound VI from compound XVIII in Preparation A.

All pharmaceutically acceptable salts, prodrugs, tautomers, hydrates and solvates of a compound of the invention is also encompassed by the invention.

A compound of the invention which is basic in nature is capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals and humans, it is often desirable in practice to initially isolate a compound of the invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as, for example, methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which can be used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

A compound of the invention which is also acidic in nature, *e.g.*, contains a COOH or tetrazole moiety, is capable of forming base salts with various pharmacologically acceptable cations. Although such salts must be pharmaceutically acceptable for administration to animals and humans, it is often desirable in practice to initially isolate a compound of the invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free acid compound by treatment with an acidic reagent, and subsequently convert the free acid to a pharmaceutically acceptable base addition salt. Examples of such pharmaceutically acceptable base addition salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts can be prepared by conventional techniques. The chemical bases which can be used as reagents to prepare the pharmaceutically acceptable base addition salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of the invention. These non-toxic base salts include salts derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

Isotopically-labeled compounds are also encompassed by the present invention. As used herein, an "isotopically-labeled compound" refers to a compound of the invention including pharmaceutical salts, prodrugs thereof, each as described herein, in which one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous,

fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

By isotopically-labeling a compound of the present invention, the compounds may be useful in drug and/or substrate tissue distribution assays. Tritiated (^{3}H) and carbon-14 (^{14}C) labeled compounds are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of the invention, including pharmaceutical salts, prodrugs thereof, can be prepared by any means known in the art.

Stereoisomers (*e.g.*, cis and trans isomers) and all optical isomers of a compound of the invention (*e.g.*, R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers are contemplated by the present invention.

The compounds, salts, prodrugs, hydrates, and solvates of the present invention can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds.

The present invention also includes atropisomers of the present invention. Atropisomers refer to compounds of the invention that can be separated into rotationally restricted isomers.

A compound of the invention, as described above, can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of a TGF-related disease state in an animal or human.

A compound of the invention is a potent inhibitor of transforming growth factor ("TGF")-β signaling pathway and are therefore of use in therapy. Accordingly, the present invention provides a method of preventing or treating a

TGF-related disease in an animal or human comprising the step of administering a therapeutically effective amount of at least one compound of the invention to the animal or human suffering from the TGF-related disease state.

As used herein, the term "therapeutically effective amount" refers to an amount of a compound of the invention required to inhibit the TGF-ß signaling pathway. As would be understood by one of skill in the art, a "therapeutically effective amount" will vary from patient to patient and will be determined on a case by case basis. Factors to consider include, but are not limited to, the patient being treated, weight, health, compound administered, etc.

There are numerous disease states that can be treated by inhibition of the TGF-ß signaling pathway. Such disease states include, but are not limited to, all types of cancer (e.g., breast, lung, colon, prostate, ovarian, pancreatic, melanoma, all hematological malignancies, etc.) as well as all types of fibrotic diseases (e.g., glomerulonephritis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis, arterial hyperplasia and restenosis, scleroderma, and dermal scarring).

The present invention also provides a pharmaceutical composition comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may be any such carrier known in the art including those described in, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co., (A. R. Gennaro edit. 1985). A pharmaceutical composition of the invention may be prepared by conventional means known in the art including, for example, mixing at least one compound of the invention with a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention may be used in the prevention or treatment of a TGF-related disease state, as described above, in an animal or human. Thus, a compound of the invention may be formulated as a pharmaceutical composition for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous), topical, or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical composition may take the form of, for example, a tablet or capsule prepared by conventional means with a

pharmaceutically acceptable excipient such as a binding agent (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); filler (*e.g.*, lactose, microcrystalline cellulose or calcium phosphate); lubricant (*e.g.*, magnesium stearate, talc or silica); disintegrant (*e.g.*, potato starch or sodium starch glycolate); or wetting agent (*e.g.*, sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of a, for example, solution, syrup or suspension, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with a pharmaceutically acceptable additive such as a suspending agent (*e.g.*, sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (*e.g.*, lecithin or acacia); non-aqueous vehicle (*e.g.*, almond oil, oily esters or ethyl alcohol); and preservative (*e.g.*, methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

A compound of the present invention may also be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397, which are herein incorporated by reference in their entirety.

A compound of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain a formulating agent such as a suspending, stabilizing and/or dispersing agent. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

A compound of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, a compound of the invention may be conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the compound of the invention. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of a compound of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of a TGF-related disease state is about 0.1 mg to about 2000 mg, preferably, about 0.1 mg to about 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains about 20μg to about 10,000μg, preferably, about 20μg to about 1000μg of a compound of the invention. The overall daily dose with an aerosol will be within the range from about 100μg to about 100 mg, preferably, about 100μg to about 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

Aerosol combination formulations for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 0.01 mg to about 1000 mg, preferably, about 0.01 mg to about 100 mg of a compound of this invention, more preferably

from about 1 mg to about 10 mg of such compound. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

Aerosol formulations for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 0.01 mg to about 20,000 mg, preferably, about 0.01 mg to about 2000 mg of a compound of the invention, more preferably from about 1 mg to about 200 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

For topical administration, a compound of the invention may be formulated as an ointment or cream.

This invention also encompasses pharmaceutical compositions containing and methods of treatment or prevention comprising administering prodrugs of at least one compound of the invention. As used herein, the term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, Calif., 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to

form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability. For example, a compound of the invention having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (*e.g.*, two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of the invention. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of a compound of the invention through the carbonyl carbon prodrug sidechain.

According to the invention, in the treatment of a TGF-related disease state, a compound of the invention, as described herein, whether alone or as part of a pharmaceutical composition may be combined with another compound(s) of the invention and/or with another therapeutic agent(s). Examples of suitable therapeutic agent(s) include, but are not limited to, standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) (*e.*g, piroxicam, diclofenac), propionic acids (*e.g.*, naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen), fenamates (*e.g.*, mefenamic acid, indomethacin, sulindac, apazone), pyrazolones (*e.g.*, phenylbutazone), salicylates (*e.g.*, aspirin), COX-2 inhibitors (*e.g.*, celecoxib, valdecoxib, rofecoxib and etoricoxib), analgesics and intraarticular therapies (*e.g.*, corticosteroids) and hyaluronic acids (*e.g.*, hyalgan and synvisc), anticancer agents (*e.g.*, endostatin and angiostatin), cytotoxic drugs (*e.g.*, adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere),alkaloids (*e.g.*, vincristine), and antimetabolites (*e.g.*, methotrexate), cardiovascular agents (*e.g.*, calcium channel blockers), lipid lowering agents (*e.g.*, statins), fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors, CNS agents (*e.g.*, as antidepressants (such as sertraline)), anti-Parkinsonian drugs (*e.g.*, deprenyl,

L-dopa, Requip, Mirapex), MAOB inhibitors (*e.g.*, selegine and rasagiline), comP inhibitors (*e.g.*, Tasmar), A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), anti-Alzheimer's drugs (*e.g.*, donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate), osteoporosis agents (*e.g.*, roloxifene, droloxifene, lasofoxifene or fosomax), and immunosuppressant agents (*e.g.*, FK-506 and rapamycin).

Biological Activity

The activity of the compounds of the invention for the various TGF-related disease states as described herein can be determined according to one or more of the following assays. According to the invention, a compound of the invention exhibits an *in vitro* IC_{50} value of less than about 10 μM. For example, the compounds of Examples 3-13 exhibit a TβRI IC_{50} value range of about 19.7-600nM.

The compounds of the present invention also possess differential activity (*i.e.* are selective for) for TβRI over TβRII and TβRIII. Selectivity is measured in standard assays as a IC_{50} ratio of inhibition in each assay.

TGF-β Type II Receptor (TβRII) Kinase Assay Protocol

Phosphorylation of myelin basic protein (MBP) by the TβRII kinase was measured as follows: 80 microliters of MBP (Upstate Biotechnology #13-104) diluted in kinase reaction buffer (KRB) containing 50 mM MOPS, 5 mM $MgCl_2$, pH 7.2 to yield a final concentration of 3 micromolar MBP was added to each well of a Millipore 96-well multiscreen-DP 0.65 micron filtration plate (#MADPNOB50). 20 microliters of inhibitor diluted in KRB was added to appropriate wells to yield the desired final concentration (10 – 0.03 micromolar). 10 microliters of a mixture of ATP (Sigma #A-5394) and ^{33}P-ATP (Perkin Elmer #NEG/602H) diluted in KRB was added to yield a final concentration of 0.25 micromolar ATP and 0.02 microcuries of ^{33}P-ATP per well. 10 microliters of a GST-TβRII fusion protein (glutathione S-transferase at the N-terminal end of the cytoplasmic domain of TβRII - amino acids 193-567 with A to V change at 438) diluted in KRB was added to each well to yield a final concentration of 27 nanomolar GST-TβRII. Plates were mixed

and incubated for 90 minutes at room temperature. After the reaction incubation, 100 microliters of cold 20% trichloroacetic acid (Aldrich #25,139-9) was added per well and plates were mixed and incubated for 60 minutes at 4°C. Liquid was then removed from the wells using a Millipore vacuum manifold. Plates were washed once with 200 microliters per well of cold 10% trichloroacetic acid followed by two washes with 100 microliters per well of cold 10% trichloroacetic acid. Plates were allowed to dry overnight at room temperature. 20 microliters of Wallac OptiPhase SuperMix scintillation cocktail was added to each well. Plates were sealed and counted using a Wallac 1450 Microbeta liquid scintillation counter. The potency of inhibitors was determined by their ability to reduce TβRII-mediated phosphorylation of the MBP substrate.

ALK-5 (TβRI) Kinase Assay Protocol

The kinase assays were performed with 65 nM GST-ALK5 and 84 nM GST-Smad3 in 50 mM HEPES, 5 mM $MgCl_2$,1 mM $CaCl_2$, 1 mM dithiothreitol, and 3 _M ATP. Reactions were incubated with 0.5 _Ci of [33 P]_ATPfor 3 h at 30°C. Phosphorylated protein was captured on P-81 paper (Whatman, Maidstone, England), washed with 0.5% phosphoric acid, and counted by liquid scintillation. Alternatively, Smad3 or Smad1 protein was also coated onto FlashPlate Sterile Basic Microplates (PerkinElmer Life Sciences, Boston, MA). Kinase assays were then performed in Flash-Plates with same assay conditions using either the kinase domain of ALK5 with Smad3 as substrate or the kinase domain of ALK6 (BMP receptor) with Smad1 as substrate. Plates were washed three times with phosphate buffer and counted by TopCount (Packard Bio-science, Meriden, CT). (Laping, N.J. et al. *Molecular Pharmacology* 62:58-64 (2002)).

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (d) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Mass Spectral data were obtained using a Micromass ZMD APCI Mass Spectrometer equipped with a Gilson gradient high performance liquid chromatograph. The following solvents and gradients were used for the analysis. Solvent A; 98% water/2% acetonirile/0.01%

formic acid and solvent B; acetonitrile containing 0.005% formic acid. Typically, a gradient was run over a period of about 4 minutes starting at 95% solvent A and ending with 100% solvent B. The mass spectrum of the major eluting component was then obtained in positive or negative ion mode scanning a molecular weight range from 165 AMU to 1100 AMU. Specific rotations were measured at room temperature using the sodium D line (589 nm). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

One of ordinary skill in the art will appreciate that in some cases protecting groups may be required during preparation. After the target molecule is made, the protecting group can be removed by methods well known to those of ordinary skill in the art, such as described in Greene and Wuts, "Protective Groups in Organic Synthesis" (2nd Ed, John Wiley & Sons 1991).

Analytical high performance liquid chromatography on reverse phase with mass spectrometry detection (LSMS) was done using Polaris 2x20 mm C18 column. Gradient elution was applied with increase of concentration of acetonitrile in 0.01 % aqueous formic acid from 5% to 100% during 3.75 min period. Mass spectrometer Micromass ZMD was used for molecular ion identification.

Example 1

Preparation of 2-(5-Benzo[1,3]dioxol-5-yl-oxazol-4-yl)-6-methyl-pyridine

Step A: To a stirred solution of benzo[1,3]dioxole-5-carbaldehyde (657 mg, 4.83 mmol) in methanol (15 mL) was added potassium carbonate (786 mg, 5.69 mmol, 1.3 equiv) and 1-isocyanomethanesulfonyl-4-methyl-benzene (863 mg, 4.38 mmol, 1 equiv). The resulting solution was heated to 70°C under a nitrogen atmosphere for 3 hours, cooled to ambient temperature, and concentrated in vacuo. The residue was

partitioned between methylene chloride and water, and the aqueous layer was extracted three times with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Silica gel chromatography (30% ethyl acetate in hexanes) provided 5-benzo[1,3]dioxol-5-yl-oxazole (676 mg, 82%).

Step B: To a -78°C solution of 5-benzo[1,3]dioxol-5-yl-oxazole (670 mg, 3.54 mmol) in dimethylformamide (5 mL) was slowly added lithium bis(trimethylsilyl)amide(3.54 mL, 1 M in THF, 3.54 mmol, 1 equiv). The reaction mixture was stirred under nitrogen atmosphere for 1 hour at -78°C, and then treated slowly with a solution of N-bromosuccinamide (630 mg, 3.54 mmol, 1 equiv) in dimethylformamide (2 mL). The resulting reaction mixture was stirred at -78°C for 1 hour, warmed to ambient temperature and poured into a mixture methylene chloride and 1 N aqueous sodium hydroxide. The aqueous layer was exctracted with methylene chloride, and the combined organics were washed with 1 N aqueous sodium hydroxide and brine, then dried over magnesium sulfate and concentrated in vacuo to provide 5-benzo[1,3]dioxol-5-yl-4-bromo-oxazole (853 mg, 90%).

Step C: A solution of 5-benzo[1,3]dioxol-5-yl-4-bromo-oxazole (156 mg, 0.58 mmol), 2-bromo-6-methyl-pyridine (100 mg, 0.58 mmol, 1 equiv), 1,1,1,2,2,2-hexamethyl-distannane (190 mg, 0.58 mmol, 1 equiv) and tetrakis(triphenylphosphine)palladium(0) (67 mg, 0.058 mmol, 0.1 equiv) in 1,4-dioxane (6 mL) was heated to reflux overnight. The resulting reaction mixture was cooled to ambient temperature and concentrated in vacuo. Silica gel chromatography (gradient from hexane to 30% ethyl acetate in hexane) provided 2-(5-Benzo[1,3]dioxol-5-yl-oxazol-4-yl)-6-methyl-pyridine (114 mg, 70%).[LCMS: Rt = 1.79 min, M+H = 281.2]

Example 2

Preparation of 2-(5-Benzo[1,3]dioxol-5-yl-oxazol-4-yl)-pyridine

To a degassed solution of 5-benzo[1,3]dioxol-5-yl-4-bromo-oxazole (50 mg, 0.19 mmol) and tetrakis(triphenylphosphine)palladium(0) (11 mg, 0.009 mmol, 0.05

equiv) in THF (2 mL) was added 2-zinc bromo -pyridine (1 mL, 0.5 M in THF, .500 mmol, 2.6 equiv). The resulting reaction mixture was heated to reflux overnight, cooled to ambient temperature, treated with saturated aqueous ammonium chloride, and diluted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride, dried over magnesium sulfate and concentrated in vacuo. Silica gel chromatography (50% ethyl acetate in hexane) provided 2-(5-Benzo[1,3]dioxol-5-yl-oxazol-4-yl)-pyridine (22.7 mg, 46 %).[LCMS: Rt = 1.79 min, M+H = 267.1]

Compounds corresponding to Examples 3-13 were prepared according to procedures analogous to those described in Examples 1 and 2.

Example 3

2-(5-Benzo[1,3]dioxol-5-yl-oxazol-4-yl)-6-methoxy-pyridine was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 2.78 min, M+H = 297.3

Example 4

2-(5-Benzo[1,3]dioxol-5-yl-oxazol-4-yl)-6-trifluoromethyl-pyridine was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 2.80 min, M+H = 335.1

Example 5

2-Methyl-5-[4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-2H-benzotriazole was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 1.63 min, M+H = 292.2

Example 6

4-[4-(6-Methyl-pyridin-2-yl)-oxazol-5-yl]-quinoline was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 1.46 min, M+H = 288.2

Example 7

1-Methyl-6-[4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-1H-benzotriazole was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 1.48 min, M+H = 292.2

Example 8

6-(4-Pyridin-2-yl-oxazol-5-yl)-quinoxaline was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 1.49 min, M+H = 275.2

Example 9

6-[4-(6-Methyl-pyridin-2-yl)-oxazol-5-yl]-quinoxaline was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 1.78 min, M+H = 289.3

Example 10

6-[4-(6-Methyl-pyridin-2-yl)-oxazol-5-yl]-quinoline was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 1.41 min, M+H = 287.9

Example 11

6-(4-pyridin-2-yl-oxazol-5-yl)-quinoline was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 1.30 min, M+H = 273.9

Example 12

2-(5-Benzo[1,3]dioxol-5-yl-oxazol-4-yl)-6-ethyl-pyridine was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 2.16 min, M+H = 295.3

Example 13

2-(5-Benzo[1,3]dioxol-5-yl-oxazol-4-yl)-6-propyl-pyridine was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 2.73 min, M+H = 309.3

Example 14

6-[4-(6-Methyl-pyridin-2-yl)-oxazol-5-yl]-benzothiazole was prepared according to procedures analogous to those described in Examples 1 and 2. Rt = 1.96 min, M+H = 294.3.

Example 15

Preparation of 2-(4-Benzo[1,3]dioxol-5-yl-oxazol-5-yl)-6-methyl-pyridine

Step A: A solution of benzo[1,3]dioxole-5-carbaldehyde (1.0 g, 6.66 mmol), 4-methyl-benzenesulfinic acid (1.1 g, 7.24 mmol, 1.09 equiv), and 10-camphorsulfonic acid (0.4 g, 1.72 mmol, 0.25 equiv) in formamide (2.8 mL) was heated to 75°C for

four hours. The resulting reaction mixture was cooled to ambient temperature, poured into a mixture of saturated aqueous sodium hydrogen carbonate (100 mL), water (100 mL), ethyl acetate (20 mL) and hexane (20 mL), and stirred at ambient temperature for 20 minutes. The resulting white solid was filtered off and azeotroped with toluene (2 x 50 mL) to provide N-[Benzo[1,3]dioxol-5-yl-(toluene-4-sulfonyl)-methyl]-formamide (740 mg, 33%).

Step B: To a solution of N-[benzo[1,3]dioxol-5-yl-(toluene-4-sulfonyl)-methyl]-formamide (740 mg, 2.22 mmol) in THF (50 mL) was slowly added phosphorous oxychloride (0.41 mL, 4.44 mmol, 2 equiv). The resulting reaction mixture was stirred at ambient temperature for 2 hours, cooled to 0°C and slowly treated with 2,6-lutidine (1.55 mL, 13.32 mmol, 6 equiv). The reaction mixture was stirred at ambient temperature for 48 hours, treated with saturated aqueous sodium hydrogen carbonate (80 mL), and then extracted with ethyl acetate (50 mL). The organics were dried over magnesium sulfate and concentrated in vacuo. Silica gel chromatography (20% ethyl acetate in hexane) provided 5-[Isocyano-(toluene-4-sulfonyl)-methyl]-benzo[1,3]dioxole as a white solid (200 mg, 29%).

Step C: A solution of 5-[isocyano-(toluene-4-sulfonyl)-methyl]-benzo[1,3]dioxole (40 mg, 0.127 mmol), 6-methyl-pyridine-2-carbaldehyde (15.4 mg, 0.127 mmol, 1 equiv) and potassium carbonate (26 mg, 0.19 mmol, 1.5 equiv) in methanol (1 mL) was shaken at 70°C for 2 hours. The reaction mixture was concentrated in vacuo, and resulting residue was partitions between water (1 mL) and methylene chloride (1 mL). The organics were purified by silica gel chromatography (20% acetone in hexane) to provide 2-(4-Benzo[1,3]dioxol-5-yl-oxazol-5-yl)-6-methyl-pyridine as a colorless oil (8 mg, 22%) [LCMS: Rt -2.34 min; M+H = 281.2].

Example 16

4-[5-(6-Methyl-pyridin-2-yl)-oxazol-4-yl]-quinoline was prepared according to a procedure analogous to that described in Example 15. [LCMS: Rt: 1.78 min; M+H = 288.2]

Example 17

1-Methyl-6-[5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-1H-benzotriazole can be prepared according to a procedure analogous to that described in Example 15.

Example 18

2-Methyl-5-[5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-2H-benzotriazole can be prepared according to a procedure analogous to that described in Example 15.

Example 19

6-[5-(6-Methyl-pyridin-2-yl)-oxazol-4-yl]-quinoline can be prepared according to a procedure analogous to that described in Example 15.

Example 20

6-[5-(6-Methyl-pyridin-2-yl)-oxazol-4-yl]-quinoxaline can be prepared according to a procedure analogous to that described in Example 15.

Example 21

2-[5-(6-Methyl-pyridin-2-yl)-oxazol-4-yl]-[1,5]naphthyridine can be prepared according to a procedure analogous to that described in Example 15.

Example 22

{4-[5-(6-Methyl-pyridin-2-yl)-oxazol-4-yl]-pyridin-2-yl}-phenyl-amine can be prepared according to a procedure analogous to that described in Example 15.

Example 23

Preparation of 2-(4-Benzo[1,3]dioxol-5-yl-2-methyl-oxazol-5-yl)-6-methyl-pyridine

Step A: To a stirred solution of benzo[1,3]dioxole-5-carboxylic acid (69 g, 415 mmol) in dimethylformamide (500 mL) was added di-imidazol-1-yl-methanone (74 g, 457 mmol, 1.1 equiv) in one portion at ambient temperature. The resulting solution was stirred at ambient temperature for 90 minutes and then treated with O,N-dimethyl-hydroxylamine hydrogen chloride (43.7 g, 457 mmol, 1.1 equiv). The reaction mixture was stirred at ambient temperature for an additional 18 hours, concentrated to 1/4 of its original volume, then poured into aqueous sodium hydrogen carbonate (5%, 1000 mL), stirred for 20 minutes, and then extracted with 2-methoxy-2-methyl-propane (2 x 300 mL). The combined organics were dried over magnesium sulfate, concentrated in vacuo, and azeotroped with toluene to provide the title compound. The crude material, benzo[1,3]dioxole-5-carboxylic

acid methoxy-methyl-amide, was used in the following step without further purification.

Step B: To a -60°C of 2,6-dimethyl-pyridine (48.3 mL, 457 mmol, 1.1 equiv) was slowly added n-butyl lithium (183 mL, 2.5 M in hexane, 457 mmol, 1.1 equiv) over 30 minutes. The resulting red solution was stirred at -60°C for an additional hour, and then treated with a solution of benzo[1,3]dioxole-5-carboxylic acid methoxy-methyl-amide (~415 mmol) in THF (200 mL) over 1 hour. The reaction was slowly warmed to -20°C over 3 hours, and then poured into ice (1 kg). The liquid layer was decanted and then washed with brine (3 x 100 mL), dried over magnesium sulfate, and concentrated in vacuo. Recrystallization from toluene provided 1-Benzo[1,3]dioxol-5-yl-2-(6-methyl-pyridin-2-yl)-ethanone (57 g, 54% over two steps).

Step C: To a stirred solution of 1-benzo[1,3]dioxol-5-yl-2-(6-methyl-pyridin-2-yl)-ethanone (2 g, 7.83 mmol) in acetic acid (15 mL) was slowly added a solution of bromine (0.40 mL, 7.83 mmol, 1 equiv) in acetic acid (5 mL). The resulting reaction mixture was stirred at ambient temperature for 1 hour and then concentrated in vacuo. The residue was stirred in diethyl ether (20 mL) and methylene chloride (10 mL) over night. A light beige solid was filtered off, providing 2-(2-Benzo[1,3]dioxol-5-yl-1-bromo-2-oxo-ethyl)-6-methyl-pyridinium bromide (3.0 g, 92%).

Step D: A solution of 2-(2-benzo[1,3]dioxol-5-yl-1-bromo-2-oxo-ethyl)-6-methyl-pyridinium bromide (150 mg, 0.36 mmol), and potassium acetate (70 mg, 0.72 mmol, 2 equiv) in dimethylformamide (2 mL) was heated to 60°C for 1 hour. The resulting reaction mixture was cooled to ambient temperature, treated with saturated aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. The organics were washed with brine, dried with magnesium sulfate and concentrated in vacuo to provide acetic acid 2-benzo[1,3]dioxol-5-yl-1-(6-methyl-pyridin-2-yl)-2-oxo-ethyl ester (80 mg, 71%).

Step E: A solution of acetic acid 2-benzo[1,3]dioxol-5-yl-1-(6-methyl-pyridin-2-yl)-2-oxo-ethyl ester (80 mg, 0.26 mmol), ammonium acetate (200 mg, 2.6 mmol, 10 equiv) in acetic acid (4 mL) was heated to 105°C for 3 hours. The resulting reaction mixture was concentrated in vacuo, and reverse phase high pressure liquid chromatography (a gradient from 5-30% acetonitrile in 0.1% aqueous formic acid) provided 2-(4-Benzo[1,3]dioxol-5-yl-2-methyl-oxazol-5-yl)-6-methyl-pyridine (15.9 mg, 21%).[LCMS: Rt = 2.10 min; M+H = 295.2]

Example 24

1-Methyl-6-[2-methyl-5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-1H-benzotriazole can be prepared according to a procedure analogous to that described in Example 23.

Example 25

2-Methyl-5-[2-methyl-5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-2H-benzotriazole can be prepared according to a procedure analogous to that described in Example 23.

Example 26

6-[2-Methyl-5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-quinoline can be prepared according to a procedure analogous to that described in Example 23.

Example 27

6-[2-Methyl-5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-quinoxaline can be prepared according to a procedure analogous to that described in Example 23.

Example 28

2-[2-Methyl-5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-[1,5]naphthyridine can be prepared according to a procedure analogous to that described in Example 23.

Example 29

{4-[2-Methyl-5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-pyridin-2-yl}-phenyl-amine can be prepared according to a procedure analogous to that described in Example 23.

Example 30

4-[2-Methyl-5-(6-methyl-pyridin-2-yl)-oxazol-4-yl]-quinoline can be prepared according to a procedure analogous to that described in Example 23.

Example 31

Preparation of 4-Benzo[1,3]dioxol-5-yl-5-(6-methyl-pyridin-2-yl)-thiazol-2-ylamine

A solution of 2-(2-benzo[1,3]dioxol-5-yl-1-bromo-2-oxo-ethyl)-6-methyl-pyridinium bromide (30 mg, 0.072 mmol), thiourea (7.5 mg, 0.094 mmol, 1.3 equiv), and potassium carbonate (0.11 mmol, 1.5 equiv) in ethanol (1 mL) was heated to 80°C overnight. The resulting reaction mixture was cooled to ambient temperature and concentrated in vacuo. Reverse phase high pressure liquid chromatography (a gradient from 5-30% acetonitrile in 0.1% aqueous formic acid) provided 4-Benzo[1,3]dioxol-5-yl-5-(6-methyl-pyridin-2-yl)-thiazol-2-ylamine (15.6 mg, 70%).[MS: M+H = 312.0].

Example 32

4-(3-Methyl-3H-benzotriazol-5-yl)-5-(6-methyl-pyridin-2-yl)-thiazol-2-ylamine can be prepared according to a procedure analogous to that described for Example 31.

Example 33

4-(2-Methyl-2H-benzotriazol-5-yl)-5-(6-methyl-pyridin-2-yl)-thiazol-2-ylamine can be prepared according to a procedure analogous to that described for Example 31.

Example 34

5-(6-Methyl-pyridin-2-yl)-4-quinolin-6-yl-thiazol-2-ylamine can be prepared according to a procedure analogous to that described for Example 31.

Example 35

5-(6-Methyl-pyridin-2-yl)-4-quinoxalin-6-yl-thiazol-2-ylamine can be prepared according to a procedure analogous to that described for Example 31.

Example 36

5-(6-Methyl-pyridin-2-yl)-4-[1,5]naphthyridin-2-yl-thiazol-2-ylamine can be prepared according to a procedure analogous to that described for Example 31.

Example 37

{4-[2-Amino-5-(6-methyl-pyridin-2-yl)-thiazol-4-yl]-pyridin-2-yl}-phenyl-amine can be prepared according to a procedure analogous to that described for Example 31.

Example 38

5-(6-Methyl-pyridin-2-yl)-4-quinolin-4-yl-thiazol-2-ylamine can be prepared according to a procedure analogous to that described for Example 31.

Example 39

Preparation of 4-(6-Methyl-pyridin-2-yl)-5-quinolin-6-yl-thiazol-2-ylamine

Step A: To a –60°C solution of 6-methyl-pyridine-2-carbaldehyde (25 g, 206 mmol) in tetrahydrofuran (200 mL) was added methyl magnesium bromide (200 mL, 1.4 M in tetrahydrofuran/toluene, 1.36 equiv) over 40 minutes. The reaction mixture was slowly warmed to -10°C over 90 minutes, and then slowly quenched with saturated aqueous ammonium chloride (75 mL). The liquid phase was decanted from the solids and concentrated in vacuo. The resulting residue was dissolved in methylene chloride, dried over magnesium sulfate, and concentrated in vacuo to yield 1-(6-Methyl-pyridin-2-yl)-ethanol (28 g, 100%).

Step B: To a -75°C solution of oxalyl chloride (20 mL, 225 mmol, 1.1 equiv) in methylene chloride (300 mL) was slowly added a solution of dimethylsulfoxide (32 mL, 2.2 equiv) in methylene chloride (400 mL) over 1 hour. The resulting solution was stirred at -75°C for 10 min,and then slowly treated with a solution of 1-(6-methyl-pyridin-2-yl)-ethanol (28 g, 204 mmol, 1 equiv) in methylene chloride (600 mL). The reaction mixture was stirred for 10 min at the same temperature, and then slowly treated with triethylamine (140 mL, 1.02 mol, 5 equiv). The resulting mixture was warmed to 20° over 2 hours, and then quenched with water (500 mL). The organic phase was separated, dried over magnesium sulfate and concentrated in vacuo to yield the crude material. Silica gel chromatography (3:1 hexanes/ethyl acetate) yielded 1-(6-Methyl-pyridin-2-yl)-ethanone (25.36 g, 92%).

Step C: To a solution of 6-chloro-quinoline (2.08 g, 12.3 mmol) in tetrahydrofuran (50 mL) was added 1-(6-methyl-pyridin-2-yl)-ethanone (2.0 g, 14.8 mmol, 1.1 equiv), palladium acetate (0.055 g, 0.25 mmol, 0.02 equiv), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (0.197 g, 0.50 mmol, 0.04 equiv), and potassium *tert*-butoxide (3.76 g, 30.75 mmol, 2.2 equiv). The resulting reaction mixture was heated to 80°C for 18 hours, then cooled down to 20°C, and slowly treated with acetic acid (3 mL). The resulting solids were filtered off, and the mother liquor was concentrated in vacuo. Silica gel chromatography (3:1

hexane/acetone) yielded 1-(6-Methyl-pyridin-2-yl)-2-quinolin-6-yl-ethanone (2.52 g, 78%).

Step D: To a stirred solution of 1-(6-methyl-pyridin-2-yl)-2-quinolin-6-yl-ethanone (1.0 g, 3.81 mmol) in acetic acid (15 mL) was slowly added a solution of bromine (0.194 ml, 3.81 mmol, 1 equiv) in acetic acid (5 mL) over 5 minutes. After stirring at the ambient temperature for 3 hours the reaction mixture was concentrated in vacuo, and to the residue dichloromethane (10 mL) and ether (60 mL) were added successively. The resulting mixture was stirred during 18 hours. The solid was filtered off and dried in vacuo, which provided 2-Bromo-1-(6-methyl-pyridin-2-yl)-2-quinolin-6-yl-ethanone hydrobromide (1.52 g, 95%).

Step E: A solution of 2-bromo-1-(6-methyl-pyridin-2-yl)-2-quinolin-6-yl-ethanone hydrobromide (24.5 mg, 0.072 mmol), thiourea (7.5 mg, 0.094 mmol, 1.3 equiv), and potassium carbonate (0.11 mmol, 1.5 equiv) in ethanol (1 mL) is heated to 80°C overnight. The resulting reaction mixture is cooled to ambient temperature and concentrated in vacuo. Reverse phase high pressure liquid chromatography (a gradient from 5-30% acetonitrile in 0.1% aqueous formic acid) provides 4-(6-Methyl-pyridin-2-yl)-5-quinolin-6-yl-thiazol-2-ylamine.

Example 40

5-(3-Methyl-3H-benzotriazol-5-yl)-4-(6-methyl-pyridin-2-yl)-thiazol-2-ylamine can be prepared according to a procedure analogous to that described in example 39.

Example 41

5-(2-Methyl-2H-benzotriazol-5-yl)-4-(6-methyl-pyridin-2-yl)-thiazol-2-ylamine can be prepared according to a procedure analogous to that described in example 39.

Example 42

5-Benzo[1,3]dioxol-5-yl-4-(6-methyl-pyridin-2-yl)-thiazol-2-ylamine can be prepared according to a procedure analogous to that described in example 39.

Example 43

4-(6-Methyl-pyridin-2-yl)-5-quinoxalin-6-yl-thiazol-2-ylamine can be prepared according to a procedure analogous to that described in example 39.

Example 44

4-(6-Methyl-pyridin-2-yl)-5-[1,5]naphthyridin-2-yl-thiazol-2-ylamine can be prepared according to a procedure analogous to that described in example 39.

Example 45

{4-[2-Amino-4-(6-methyl-pyridin-2-yl)-thiazol-5-yl]-pyridin-2-yl}-phenyl-amine can be prepared according to a procedure analogous to that described in example 39.

Example 46

4-(6-Methyl-pyridin-2-yl)-5-quinolin-4-yl-thiazol-2-ylamine can be prepared according to a procedure analogous to that described in example 39.

Example 47

Preparation of 6-[2-Methyl-4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-quinoline

Step A: A solution of of 2-bromo-1-(6-methyl-pyridin-2-yl)-2-quinolin-6-yl-ethanone hydrobromide (94 mg, 0.36 mmol), and potassium acetate (70 mg, 0.72 mmol, 2 equiv) in dimethylformamide (2 mL) is heated to 60°C for 1 hour. The resulting reaction mixture is cooled to ambient temperature, treated with saturated aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. The organics are washed with brine, dried with magnesium sulfate and concentrated in vacuo to provide acetic acid 2-(6-methyl-pyridin-2-yl)-2-oxo-1-quinolin-6-yl-ethyl ester.

Step B: A solution of acetic acid 2-(6-methyl-pyridin-2-yl)-2-oxo-1-quinolin-6-yl-ethyl ester (83 mg, 0.26 mmol), ammonium acetate (200 mg, 2.6 mmol, 10 equiv) in acetic acid (4 mL) is heated to 105°C for 3 hours. The resulting reaction mixture is concentrated in vacuo, and reverse phase high pressure liquid chromatography (a gradient from 5-30% acetonitrile in 0.1% aqueous formic acid) provides 6-[2-Methyl-4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-quinoline.

Example 48

1-Methyl-6-[2-methyl-4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-1H-benzotriazole can be prepared according to a procedure analogous to that described in Example 47.

Example 49

2-Methyl-5-[2-methyl-4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-2H-benzotriazole can be prepared according to a procedure analogous to that described in Example 47.

Example 50

2-(5-Benzo[1,3]dioxol-5-yl-2-methyl-oxazol-4-yl)-6-methyl-pyridine can be prepared according to a procedure analogous to that described in Example 47.

Example 51

6-[2-Methyl-4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-quinoxaline can be prepared according to a procedure analogous to that described in Example 47.

Example 52

2-[2-Methyl-4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-[1,5]naphthyridine can be prepared according to a procedure analogous to that described in Example 47.

Example 53

{4-[2-Methyl-4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-pyridin-2-yl}-phenyl-amine can be prepared according to a procedure analogous to that described in Example 47.

Example 54

4-[2-Methyl-4-(6-methyl-pyridin-2-yl)-oxazol-5-yl]-quinoline can be prepared according to a procedure analogous to that described in Example 47.

The following examples 55-70 can be prepared according to a procedure analogous to that described in Examples 30 and 38 with replacing thiourea with thioformamide (Ronald H. Rynbrandt, Edward E. Nishizawa, Doris P. Balogoyen, A. Rene Mendoza, and Kathleen A. Annis, *J. Med. Chem.*, Vol 24, 1507-1510 (1981)).

Example 55

1-Methyl-6-[4-(6-methyl-pyridin-2-yl)-thiazol-5-yl]-1H-benzotriazole

Example 56

2-Methyl-5-[4-(6-methyl-pyridin-2-yl)-thiazol-5-yl]-2H-benzotriazole

Example 57

2-(5-Benzo[1,3]dioxol-5-yl-thiazol-4-yl)-6-methyl-pyridine

Example 58

6-[4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-quinoxaline

Example 59

2-[4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-[1,5]naphthyridine

Example 60

{4-[4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-pyridin-2-yl}-phenyl-amine

Example 61

4-[4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-quinoline

Example 62

6-[4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-quinoline

Example 63

1-Methyl-6-[5-(6-methyl-pyridin-2-yl)-thiazol-4-yl]-1H-benzotriazole

Example 64

2-Methyl-5-[5-(6-methyl-pyridin-2-yl)-thiazol-4-yl]-2H-benzotriazole

Example 65

2-(4-Benzo[1,3]dioxol-5-yl-thiazol-5-yl)-6-methyl-pyridine

Example 66

6-[5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-quinoxaline

Example 67

2-[5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-[1,5]naphthyridine

Example 68

{4-[5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-pyridin-2-yl}-phenyl-amine

Example 69

4-[5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-quinoline

Example 70

6-[5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-quinoline

The following examples 71-86 can be prepared according to a procedure analogous to that described in Examples 31 and 39 with replacing thiourea with thioacetamide (I. Moreno, I. Tellitu, R. SanMartin, D. Badfa, L. Carrillo, and E. Dominguez, *Tetrahedron Letters,* Vol. 40, 5067-5070 (1999); Ronald H. Rynbrandt, Edward E. Nishizawa, Doris P. Balogoyen, A. Rene Mendoza, and Kathleen A. Annis, *J. Med. Chem.*, Vol 24, 1507-1510 (1981)).

Example 71

1-Methyl-6-[2-methyl-4-(6-methyl-pyridin-2-yl)-thiazol-5-yl]-1H-benzotriazole

Example 72

2-Methyl-5-[2-methyl-4-(6-methyl-pyridin-2-yl)-thiazol-5-yl]-2H-benzotriazole

Example 73

2-(5-Benzo[1,3]dioxol-5-yl-2-methyl-thiazol-4-yl)-6-methyl- pyridine

Example 74

6-[2-methyl-4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-quinoxaline

Example 75

2-[2-methyl-4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-[1,5]naphthyridine

Example 76

{4-[2-methyl-4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-pyridin-2-yl}-phenyl-amine

Example 77

4-[2-methyl-4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-quinoline

Example 78

6-[2-methyl-4-(6-Methyl-pyridin-2-yl)-thiazol-5-yl]-quinoline

Example 79

1-Methyl-6-[2-methyl-5-(6-methyl-pyridin-2-yl)-thiazol-4-yl]-1H-benzotriazole

Example 80

2-Methyl-5-[2-methyl-5-(6-methyl-pyridin-2-yl)-thiazol-4-yl]-2H-benzotriazole

Example 81

2-(4-Benzo[1,3]dioxol-5-yl-2-methyl-thiazol-5-yl)-6-methyl-pyridine

Example 82

6-[2-methyl-5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-quinoxaline

Example 83

2-[2-methyl-5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-[1,5]naphthyridine

Example 84

{4-[2-methyl-5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-pyridin-2-yl}-phenyl-amine

Example 85

4-[2-methyl-5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-quinoline

Example 86

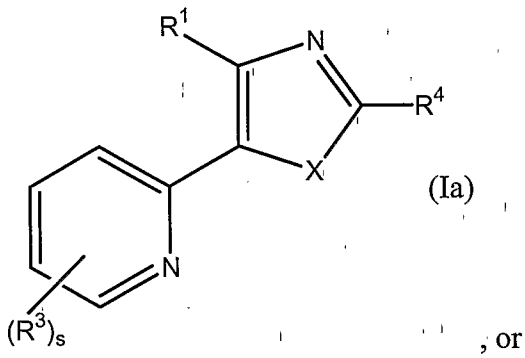
6-[2-methyl-5-(6-Methyl-pyridin-2-yl)-thiazol-4-yl]-quinoline

All publications, including but not limited to, issued patents, patent applications, and journal articles, cited in this application are each herein incorporated by reference in their entirety.

Although the invention has been described above with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

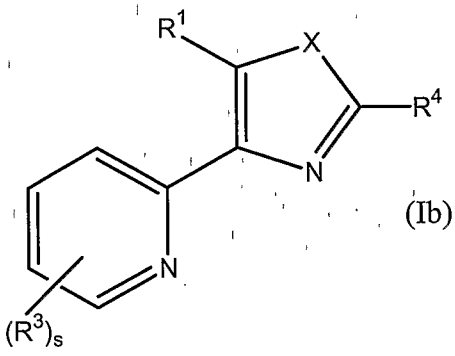
The claimed invention is:

1. A compound of formula (Ia) or (Ib):



(Ia)

, or



(Ib)

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

X is O or S;

R^1 is a saturated, unsaturated, or aromatic C_3-C_{20} mono-, bi- or polycyclic ring optionally containing at least one heteroatom selected from the group consisting of N, O and S, wherein R^1 can optionally be further independently substituted with at least one moiety independently selected from the group consisting of: carbonyl, halo, halo(C_1-C_6)alkyl, perhalo(C_1-C_6)alkyl, perhalo(C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, oxo, mercapto, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, (C_5-C_{10})aryl or (C_5-C_{10})heteroaryl, (C_5-C_{10})aryloxy or (C_5-C_{10})heteroaryloxy, (C_5-C_{10})ar(C_1-C_6)alkyl or (C_5-C_{10})heteroar(C_1-C_6)alkyl, (C_5-C_{10})ar(C_1-C_6)alkoxy or (C_5-C_{10})heteroar(C_1-C_6)alkoxy, HO-(C=O)-, ester, amido, ether, amino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl,

di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_5-C_{10})heterocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkyl- and di(C_1-C_6)alkylamino, cyano, nitro, carbamoyl, (C_1-C_6)alkylcarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_5-C_{10})arylcarbonyl, (C_5-C_{10})aryloxycarbonyl, (C_1-C_6)alkylsulfonyl, and (C_5-C_{10})arylsulfonyl;

each R^3 is independently selected from the group consisting of: hydrogen, halo, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_5-C_{10})heteroaryl, (C_5-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_5-C_{10})heteroaryl-O-, (C_5-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, O_2N-, NC-, amino, $Ph(CH_2)_{1-6}HN$-, (C_1-C_6)alkyl HN-, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, amino(C=O)-, aminoO_2S-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[(((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_5-C_{10})heteroaryl-(C=O)-, (C_5-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_5-C_{10})heteroaryl-NH-(C=O)-, (C_5-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)- and (C_1-C_6)alkyl-(C=O)-O-,

where alkyl, alkenyl, alkynyl, phenyl, heteroaryl, heterocyclic, cycloalkyl, alkoxy, phenoxy, amino of R^3 is optionally substituted by at least one substituent independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo, H_2N-, $Ph(CH_2)_{1-6}HN$-, and (C_1-C_6)alkylHN-;

s is an integer from one to five;

R^4 is independently selected from the group consisting of: hydrogen, halo, halo(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_5-C_{10})heteroaryl, (C_5-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy,

$(C_1\text{-}C_6)$alkoxy, perhalo$(C_1\text{-}C_6)$alkoxy, phenoxy, $(C_5\text{-}C_{10})$heteroaryl-O-, $(C_5\text{-}C_{10})$heterocyclic-O-, $(C_3\text{-}C_{10})$cycloalkyl-O-, $(C_1\text{-}C_6)$alkyl-S-, $(C_1\text{-}C_6)$alkyl-SO_2-, $(C_1\text{-}C_6)$alkyl-NH-SO_2-, O_2N-, NC-, amino, $Ph(CH_2)_{1\text{-}6}HN$-, $(C_1\text{-}C_6)$alkylHN-, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)alkyl]_2$-amino, $(C_1\text{-}C_6)$alkyl-SO_2-NH-, amino(C=O)-, aminoO$_2$S-, $(C_1\text{-}C_6)$alkyl-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-(C=O)-$((C_1\text{-}C_6)$alkyl)-N-, phenyl-(C=O)-NH-, phenyl-(C=O)-$((C_1\text{-}C_6)$alkyl)-N]-, $(C_1\text{-}C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_5\text{-}C_{10})$heteroaryl-(C=O)-, $(C_5\text{-}C_{10})$heterocyclic-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-(C=O)-, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, H_2N(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $((C_1\text{-}C_6)alkyl)_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $(C_5\text{-}C_{10})$heteroaryl-NH-(C=O)-, $(C_5\text{-}C_{10})$heterocyclic-NH-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-NH-(C=O)- and $(C_1\text{-}C_6)$alkyl-(C=O)-O-,

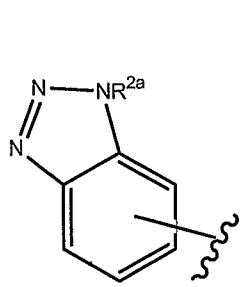
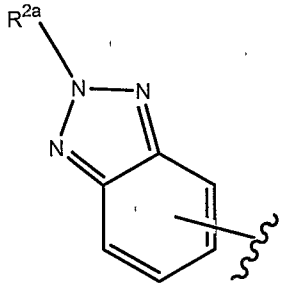
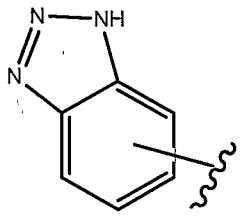
where alkyl, alkenyl, alkynyl, phenyl, heteroaryl, heterocyclic, cycloalkyl, alkoxy, phenoxy, amino of R^4 is optionally substituted by at least one substituent independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, halo, H_2N-, Ph $(CH_2)_{1\text{-}6}HN$-, $(C_1\text{-}C_6)$alkylHN-, $(C_5\text{-}C_{10})$heteroary and $(C_5\text{-}C_{10})$heterocyclyl;

with the proviso that when R^4 is a substituted phenyl moiety, then (a) R^1 is not naphthyl, phenyl or anthracenyl and (b) if R^1 is a phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to three heteroatoms independently selected from N, O and S, then the fused cyclic ring of said R^1 moiety is substituted;

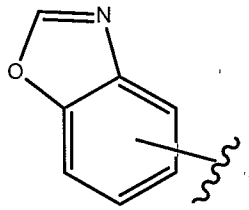
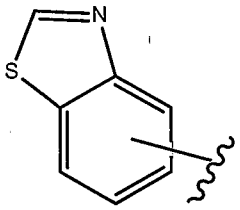
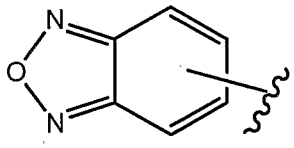
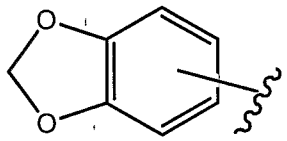
with the proviso that when R^4 is NH_2 and X is S, then R^1 is not an amino-substituted pyridyl or pyrimidinyl moiety; and

with the provisio that when in formula (Ia) R^4 is CH_3 and X is S, R^1 is not a 3,4-dimethoxy substituted phenyl moiety .

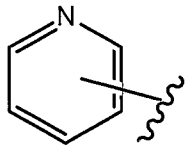
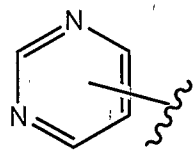
2. A compound of claim 1, wherein R^1 is




, or .

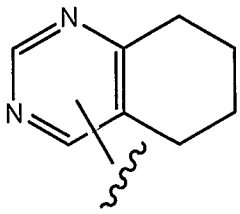
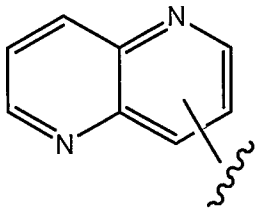
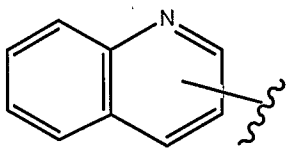
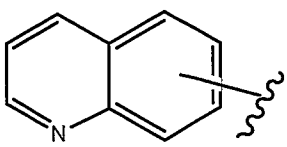
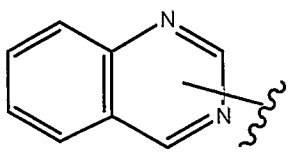
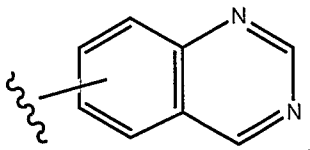
3. A compound of claim 1, wherein R^1 is





or .

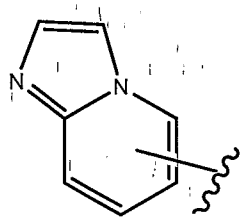
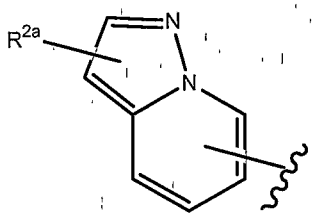
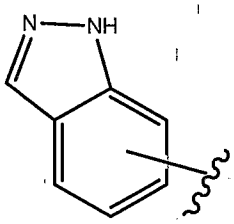
4. A compound of claim 1, wherein R^1 is



or .

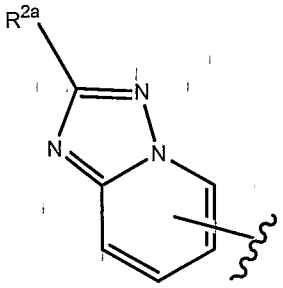
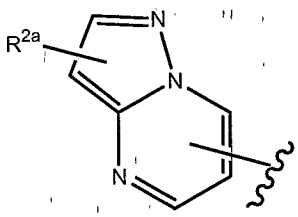
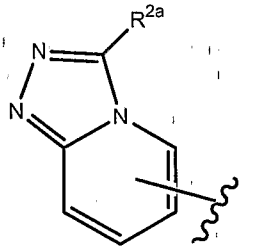
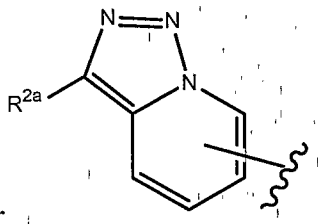
5. A compound of claim 1, wherein R^1 is







, or .

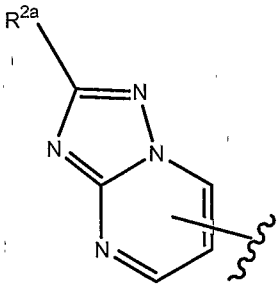
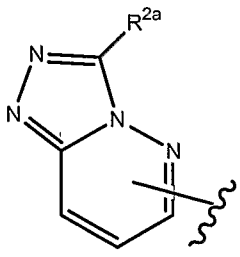
6. A compound of claim 1, wherein R^1 is


,

, or

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7. A compound of claim 1, wherein R^1 is


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,

,

or .

8. A compound of claim 1, wherein R^1 is


or

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9. A compound of claim 1, wherein X is O; s is one to two; R^3 is hydrogen or $(C_1\text{-}C_6)$alkyl; and R^4 is H, $(C_1\text{-}C_6)$alkyl, or amino.

10. A compound of claim 1, wherein X is S; s is one to two; R^3 is hydrogen or $(C_1$-$C_6)$alkyl; and R^4 is H, $(C_1$-$C_6)$alkyl, or amino.

11. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A method of preventing or treating a TGF-related disease state in an animal or human comprising the step of administering a therapeutically effective amount of a compound of claim 1 to the animal or human suffering from the TGF-related disease state.

13. A method of claim 12, wherein said TGF-related disease state is selected from the group consisting of cancer, glomerulonephritis, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis, intimal hyperplasia and restenosis, scleroderma, and dermal scarring.