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(54) Title: PROCESS FOR PREPARING [(3-HYDROXYPYRIDINE-2-CARBONYL)AMINO]ALKANOIC ACIDS, ESTERS AND AMIDES

(57) Abstract: Disclosed are processes for preparing [(3-hydroxypyridine-2-carbonyl)amino]-alkanoic acids, derivatives, inter alia, 5-aryl substituted and 5-heteroaryl substituted [(3-hydroxypyridine-2-carbonyl]amino} acetic acids. Further disclosed are methods for making prodrugs of [(3-hydroxypyridine-2-carbonyl)-amino]acetic acids, for example, [(3-hydroxypyridine-2-carbonyl]amino}acetic acid esters and {[3-hydroxypyridine-2-carbonyl]amino} acetic acid amides. The disclosed compounds are useful as prolyl hydroxylase inhibitors or for treating conditions wherein prolyl hydroxylase inhibition is desired.

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PROCESS FOR PREPARING [(3-HYDROXYPYRIDINE-2-CARBONYL)AMINO]ALKANOIC ACIDS, ESTERS AND AMIDES

PRIORITY

This Application claims priority from U.S. Provisional Application Serial No. 61/493,536, filed June 6, 2011, the entirety of which is included herein by reference.

FIELD

Disclosed are processes for preparing [(3-hydroxypyridine-2-carbonyl)amino]-alkanoic acids, derivatives, *inter alia*, 5-aryl substituted and 5- heteroaryl substituted [(3-hydroxypyridine-2-carbonyl]amino}acetic acids. Further disclosed are methods for making prodrugs of [(3-hydroxypyridine-2-carbonyl)-amino]acetic acids, for example, [(3-hydroxypyridine-2-carbonyl]amino}acetic acid esters and {[3-hydroxypyridine-2-carbonyl]amino}acetic acid amides. The disclosed compounds are useful as prolyl hydroxylase inhibitors or for treating conditions wherein prolyl hydroxylase inhibition is desired.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts an outline of one embodiment for preparing the disclosed prolyl hydroxylase inhibitors.

Figure 2 depicts an outline of one embodiment for preparing the disclosed prolyl hydroxylase inhibitor ester prodrugs.

Figure 3 depicts an outline of one embodiment for preparing the disclosed prolyl hydroxylase inhibitor amide prodrugs.

DETAILED DISCLOSURE

The materials, compounds, compositions, articles, and methods described herein may be understood more readily by reference to the following detailed description of specific aspects of the disclosed subject matter and the Examples included therein.

Before the present materials, compounds, compositions, articles, devices, and methods are disclosed and described, it is to be understood that the aspects described below are not limited to specific synthetic methods or specific reagents, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting.

Also, throughout this specification, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which the disclosed matter pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

General Definitions

In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (^{O}C) unless otherwise specified.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the relevant active compound without causing clinically unacceptable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

A weight percent of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

“Admixture” or “blend” is generally used herein means a physical combination of two or more different components.

Throughout the description and claims of this specification the word “comprise” and other forms of the word, such as “comprising” and “comprises,” means including but not limited to, and is not intended to exclude, for example, other additives, components, integers, or steps.

As used in the description and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “[(3-hydroxypyridine-2-carbonyl)amino]alkanoic acid” includes mixtures of two or more such [(3-hydroxypyridine-2-carbonyl)amino]alkanoic acids, reference to “the compound” includes mixtures of two or more such compounds, which can include mixtures of optical isomers (racemic mixtures), and the like.

“Optional” or “optionally” means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that when a value is disclosed, then "less than or equal to" the value, "greater than or equal to the value," and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value "10" is disclosed, then "less than or equal to 10" as well as "greater than or equal to 10" is also disclosed. It is also understood that throughout the application data are provided in a number of different formats and that this data represent endpoints and starting points and ranges for any combination of the data points. For example, if a particular data point "10" and a particular data point "15" are disclosed, it is understood that greater than, greater than or equal to, less than, less than or equal to, and equal to 10 and 15 are considered disclosed as well as between 10 and 15. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

The following chemical hierarchy is used throughout the specification to describe and enable the scope of the present disclosure and to particularly point out and distinctly claim the units which comprise the compounds of the present disclosure, however, unless otherwise specifically defined, the terms used herein are the same as those of the artisan of ordinary skill. The term "hydrocarbyl" stands for any carbon atom-based unit (organic molecule), said units optionally containing one or more organic functional group, including inorganic atom comprising salts, *inter alia*, carboxylate salts, quaternary ammonium salts. Within the broad meaning of the term "hydrocarbyl" are the classes "acyclic hydrocarbyl" and "cyclic hydrocarbyl" which terms are used to divide hydrocarbyl units into cyclic and non-cyclic classes.

As it relates to the following definitions, "cyclic hydrocarbyl" units can comprise only carbon atoms in the ring (*i.e.*, carbocyclic and aryl rings) or these units can comprise one or more heteroatoms in the ring (*i.e.*, heterocyclic and heteroaryl rings). For "carbocyclic" rings the lowest number of carbon atoms in a ring is 3 carbon atoms; cyclopropyl. For "aryl" rings the lowest number of carbon atoms in a ring are 6 carbon atoms; phenyl. For "heterocyclic" rings the lowest number of carbon atoms in a ring is 1 carbon atom; diazirinyl, a C_1 heterocyclic ring. Ethylene oxide comprises 2 carbon atoms and is a C_2 heterocyclic ring. For "heteroaryl" rings the lowest number of carbon atoms in a ring is 1 carbon atom; 1,2,3,4-tetrazolyl, a C_1 heteroaryl ring. The terms "heterocycle" and "heterocyclic ring" can also include "heteroaryl rings." The following is a non-limiting description of the units encompassed by the terms "acyclic hydrocarbyl" and "cyclic hydrocarbyl" as used herein.

A. Substituted and unsubstituted acyclic hydrocarbyl:

For the purposes of the present disclosure the term "substituted and unsubstituted acyclic hydrocarbyl" encompasses 3 categories of units:

1) linear or branched alkyl, non-limiting examples of which include, methyl (C_1), ethyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), and the like; substituted linear or branched alkyl, non-limiting examples of which includes, hydroxymethyl (C_1), chloromethyl (C_1), trifluoromethyl (C_1), aminomethyl (C_1), 1-chloroethyl (C_2), 2-hydroxyethyl (C_2), 1,2-difluoroethyl (C_2), 3-carboxypropyl (C_3), and the like.

2) linear or branched alkenyl, non-limiting examples of which include, ethenyl (C_2), 3-propenyl (C_3), 1-propenyl (*also* 2-methylethenyl) (C_3), isopropenyl (*also* 2-methylethen-2-yl) (C_3), buten-4-yl (C_4), and the like; substituted linear or branched alkenyl, non-limiting examples of which include, 2-chloroethenyl (*also* 2-chlorovinyl) (C_2), 4-hydroxybuten-1-yl (C_4), 7-hydroxy-7-methyloct-4-en-2-yl (C_9), 7-hydroxy-7-methyloct-3,5-dien-2-yl (C_9), and the like.

3) linear or branched alkynyl, non-limiting examples of which include, ethynyl (C_2), prop-2-ynyl (*also* propargyl) (C_3), propyn-1-yl (C_3), and 2-methyl-hex-4-yn-1-yl (C_7); substituted linear or branched alkynyl, non-limiting examples of which include, 5-hydroxy-5-methylhex-3-ynyl (C_7), 6-hydroxy-6-methylhept-3-yn-2-yl (C_8), 5-hydroxy-5-ethylhept-3-ynyl (C_9), and the like.

B. Substituted and unsubstituted cyclic hydrocarbyl:

For the purposes of the present disclosure the term "substituted and unsubstituted cyclic hydrocarbyl" encompasses 5 categories of units:

1) The term “carbocyclic” is defined herein as “encompassing rings comprising from 3 to 20 carbon atoms, in one embodiment from 3 to 10 carbon atoms, in another embodiment from 3 to 7 carbon atoms, in a still further embodiment 5 or 6 carbon atoms, wherein the atoms which comprise said rings are limited to carbon atoms, and further each ring can be independently substituted with one or more moieties capable of replacing one or more hydrogen atoms.” The following are non-limiting examples of “substituted and unsubstituted carbocyclic rings” which encompass the following categories of units:

i) carbocyclic rings having a single substituted or unsubstituted hydrocarbon ring, non-limiting examples of which include, cyclopropyl (C_3), 2-methyl-cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), 2,3-dihydroxycyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclopentadienyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cycloheptyl (C_7), cyclooctanyl (C_8), 2,5-dimethylcyclopentyl (C_5), 3,5-dichlorocyclohexyl (C_6), 4-hydroxycyclohexyl (C_6), and 3,3,5-trimethylcyclohex-1-yl (C_6).

ii) carbocyclic rings having two or more substituted or unsubstituted fused hydrocarbon rings, non-limiting examples of which include, octahydropentalenyl (C_8), octahydro-1*H*-indenyl (C_9), 3a,4,5,6,7,7a-hexahydro-3*H*-inden-4-yl (C_9), decahydroazulenyl (C_{10}).

iii) carbocyclic rings which are substituted or unsubstituted bicyclic hydrocarbon rings, non-limiting examples of which include, bicyclo-[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, 1,3-dimethyl[2.2.1]heptan-2-yl, bicyclo[2.2.2]octanyl, and bicyclo[3.3.3]undecanyl.

2) The term “aryl” is defined herein as “units encompassing at least one phenyl or naphthyl ring and wherein there are no heteroaryl or heterocyclic rings fused to the phenyl or naphthyl ring and further each ring can be independently substituted with one or more moieties capable of replacing one or more hydrogen atoms.” The following are non-limiting examples of “substituted and unsubstituted aryl rings” which encompass the following categories of units:

i) C_6 or C_{10} substituted or unsubstituted aryl rings; phenyl and naphthyl rings whether substituted or unsubstituted, non-limiting examples of which include, phenyl (C_6), naphthylen-1-yl (C_{10}), naphthylen-2-yl (C_{10}), 4-fluorophenyl (C_6), 2-hydroxyphenyl (C_6), 3-methylphenyl (C_6), 2-amino-4-fluorophenyl (C_6), 2-(*N*,*N*-

diethylamino)phenyl (C_6), 2-cyanophenyl (C_6), 2,6-di-*tert*-butylphenyl (C_6), 3-methoxyphenyl (C_6), 8-hydroxynaphthylen-2-yl (C_{10}), 4,5-dimethoxynaphthylen-1-yl (C_{10}), and 6-cyano-naphthylen-1-yl (C_{10}).

ii) C_6 or C_{10} aryl rings fused with 1 or 2 saturated rings to afford C_8-C_{20} ring systems, non-limiting examples of which include, bicyclo[4.2.0]octa-1,3,5-trienyl (C_8), and indanyl (C_9).

3) The terms "heterocyclic" and/or "heterocycle" are defined herein as "units comprising one or more rings having from 3 to 20 atoms wherein at least one atom in at least one ring is a heteroatom chosen from nitrogen (N), oxygen (O), or sulfur (S), or mixtures of N, O, and S, and wherein further the ring which contains the heteroatom is also not an aromatic ring." The following are non-limiting examples of "substituted and unsubstituted heterocyclic rings" which encompass the following categories of units:

i) heterocyclic units having a single ring containing one or more heteroatoms, non-limiting examples of which include, diazirinyl (C_1), aziridinyl (C_2), urazolyl (C_2), azetidinyl (C_3), pyrazolidinyl (C_3), imidazolidinyl (C_3), oxazolidinyl (C_3), isoxazolinyl (C_3), thiazolidinyl (C_3), isothiazolinyl (C_3), oxathiazolidinonyl (C_3), oxazolidinonyl (C_3), hydantoinyl (C_3), tetrahydrofuranyl (C_4), pyrrolidinyl (C_4), morpholinyl (C_4), piperazinyl (C_4), piperidinyl (C_4), dihydropyranyl (C_5), tetrahydropyranyl (C_5), piperidin-2-onyl (valerolactam) (C_5), 2,3,4,5-tetrahydro-1*H*-azepinyl (C_6), 2,3-dihydro-1*H*-indole (C_8), and 1,2,3,4-tetrahydroquinoline (C_9).

ii) heterocyclic units having 2 or more rings one of which is a heterocyclic ring, non-limiting examples of which include hexahydro-1*H*-pyrrolizinyl (C_7), 3a,4,5,6,7,7a-hexahydro-1*H*-benzo[d]imidazolyl (C_7), 3a,4,5,6,7,7a-hexahydro-1*H*-indolyl (C_8), 1,2,3,4-tetrahydroquinolinyl (C_9), and decahydro-1*H*-cycloocta[b]pyrrolyl (C_{10}).

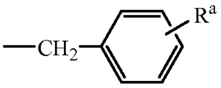
4) The term "heteroaryl" is defined herein as "encompassing one or more rings comprising from 5 to 20 atoms wherein at least one atom in at least one ring is a heteroatom chosen from nitrogen (N), oxygen (O), or sulfur (S), or mixtures of N, O, and S, and wherein further at least one of the rings which comprises a heteroatom is an aromatic ring." Heteroaryl rings can comprise from 1 to 19 carbon atoms, in another embodiment heteroaryl rings can comprise from 1 to 9 carbon atoms. The

following are non-limiting examples of "substituted and unsubstituted heterocyclic rings" which encompass the following categories of units:

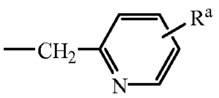
i) heteroaryl rings containing a single ring, non-limiting examples of which include, 1,2,3,4-tetrazolyl (C_1), [1,2,3]triazolyl (C_2), [1,2,4]triazolyl (C_2), triazinyl (C_3), thiazolyl (C_3), 1*H*-imidazolyl (C_3), oxazolyl (C_3), isoxazolyl (C_3), isothiazolyl (C_3), furanyl (C_4), thiophenyl (C_4), pyrimidinyl (C_4), 2-phenylpyrimidinyl (C_4), pyridinyl (C_5), 3-methylpyridinyl (C_5), and 4-dimethylaminopyridinyl (C_5)

ii) heteroaryl rings containing 2 or more fused rings one of which is a heteroaryl ring, non-limiting examples of which include: 7*H*-purinyl (C_5), 9*H*-purinyl (C_5), 6-amino-9*H*-purinyl (C_5), 5*H*-pyrrolo[3,2-*d*]pyrimidinyl (C_6), 7*H*-pyrrolo[2,3-*d*]pyrimidinyl (C_6), pyrido[2,3-*d*]pyrimidinyl (C_7), 2-phenylbenzo[d]thiazolyl (C_7), 1*H*-indolyl (C_8), 4,5,6,7-tetrahydro-1-*H*-indolyl (C_8), quinoxalinyl (C_8), 5-methylquinoxalinyl (C_8), quinazolinyl (C_8), quinolinyl (C_9), 8-hydroxy-quinolinyl (C_9), and isoquinolinyl (C_9).

5) C_1-C_6 tethered cyclic hydrocarbyl units (whether carbocyclic units, C_6 or C_{10} aryl units, heterocyclic units, or heteroaryl units) which connected to another moiety, unit, or core of the molecule by way of a C_1-C_6 alkylene unit. Non-limiting examples of tethered cyclic hydrocarbyl units include benzyl C_1-(C_6) having the formula:



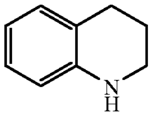
wherein R^a is optionally one or more independently chosen substitutions for hydrogen. Further examples include other aryl units, *inter alia*, (2-hydroxyphenyl)hexyl C_6-(C_6); naphthalen-2-ylmethyl C_1-(C_{10}), 4-fluorobenzyl C_1-(C_6), 2-(3-hydroxyphenyl)ethyl C_2-(C_6), as well as substituted and unsubstituted C_3-C_{10} alkylenecarbocyclic units, for example, cyclopropylmethyl C_1-(C_3), cyclopentylethyl C_2-(C_5), cyclohexylmethyl C_1-(C_6);. Included within this category are substituted and unsubstituted C_1-C_{10} alkylene-heteroaryl units, for example a 2-picolyl C_1-(C_6) unit having the formula:



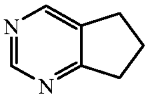
wherein R^a is the same as defined above. In addition, C_1-C_{12} tethered cyclic hydrocarbyl units include C_1-C_{10} alkyleneheterocyclic units and alkylene-heteroaryl units, non-limiting examples of which include, aziridinylmethyl C_1-(C_2) and oxazol-2-ylmethyl C_1-(C_3).

For the purposes of the present disclosure carbocyclic rings are from C_3 to C_{20}; aryl rings are C_6 or C_{10}; heterocyclic rings are from C_1 to C_9; and heteroaryl rings are from C_1 to C_9.

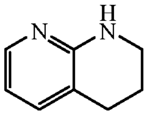
For the purposes of the present disclosure, and to provide consistency in defining the present disclosure, fused ring units, as well as spirocyclic rings, bicyclic rings and the like, which comprise a single heteroatom will be characterized and referred to herein as being encompassed by the cyclic family corresponding to the heteroatom containing ring, although the artisan may have alternative characterizations. For example, 1,2,3,4-tetrahydroquinoline having the formula:



is, for the purposes of the present disclosure, defined as a heterocyclic unit. 6,7-Dihydro-5*H*-cyclopentapyrimidine having the formula:



is, for the purposes of the present disclosure, is defined as a heteroaryl unit. When a fused ring unit contains heteroatoms in both a non-aromatic ring (heterocyclic ring) and an aryl ring (heteroaryl ring), the aryl ring will predominate and determine the type of category to which the ring is assigned herein for the purposes of describing the invention. For example, 1,2,3,4-tetrahydro-[1,8]naphthpyridine having the formula:



is, for the purposes of the present disclosure, is defined as a heteroaryl unit.

The term "substituted" is used throughout the specification. The term "substituted" is applied to the units described herein as "substituted unit or moiety is a hydrocarbyl unit or moiety, whether acyclic or cyclic, which has one or more hydrogen atoms replaced by a substituent or several substituents as defined herein below." The units, when substituting for hydrogen atoms are capable of replacing one hydrogen atom, two hydrogen atoms, or three hydrogen atoms of a hydrocarbyl moiety at a time. In addition, these substituents can replace two hydrogen atoms on two adjacent carbons to form said substituent, new moiety, or unit. For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. Three hydrogen replacement includes cyano, and the like. The term substituted is used throughout the present specification to indicate that a hydrocarbyl moiety, *inter alia*, aromatic ring, alkyl chain; can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, 4-hydroxyphenyl is a "substituted aromatic carbocyclic ring (aryl ring)", (N,N-dimethyl-5-amino)octanyl is a " substituted C_8 linear alkyl unit, 3-guanidinopropyl is a "substituted C_3 linear alkyl unit," and 2-carboxypyridinyl is a "substituted heteroaryl unit."

The following are non-limiting examples of units which can substitute for hydrogen atoms on a carbocyclic, aryl, heterocyclic, or heteroaryl unit:

i) substituted or unsubstituted C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl; methyl (C_1), ethyl (C_2), ethenyl (C_2), ethynyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), 3-propenyl (C_3), 1-propenyl (*also* 2-methylethenyl) (C_3), isopropenyl (*also* 2-methylethen-2-yl) (C_3), prop-2-ynyl (*also* propargyl) (C_3), propyn-1-yl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), buten-4-yl (C_4), cyclopentyl (C_5), cyclohexyl (C_6);

ii) substituted or unsubstituted C_6 or C_{10} aryl; for example, phenyl, naphthyl (also referred to herein as naphthylen-1-yl (C_{10}) or naphthylen-2-yl (C_{10}));

iii) substituted or unsubstituted C_7 or C_{11} alkylenearyl; for example, benzyl, 2-phenylethyl, naphthylen-2-ylmethyl;

iv) substituted or unsubstituted C_1-C_9 heterocyclic rings; as described herein below;

v) substituted or unsubstituted C_1-C_9 heteroaryl rings; as described herein below;

vi) $-(CR^{102a}R^{102b})_aOR^{101}$; for example, $-OH$, $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_2CH_3$, $-OCH_2CH_2CH_3$, and $-CH_2OCH_2CH_2CH_3$;

vii) $-(CR^{102a}R^{102b})_aC(O)R^{101}$; for example, $-COCH_3$, $-CH_2COCH_3$, $-COCH_2CH_3$, $-CH_2COCH_2CH_3$, $-COCH_2CH_2CH_3$, and $-CH_2COCH_2CH_2CH_3$;

viii) $-(CR^{102a}R^{102b})_aC(O)OR^{101}$; for example, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CH_2CO_2CH_2CH_2CH_3$;

ix) $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$; for example, $-CONH_2$, $-CH_2CONH_2$, $-CONHCH_3$, $-CH_2CONHCH_3$, $-CON(CH_3)_2$, and $-CH_2CON(CH_3)_2$;

x) $-(CR^{102a}R^{102b})_aN(R^{101})\,C(O)R^{101}$; for example, $-NHCOCH_3$, $-CH_2NHCOCH_3$, $-NHCOCH_2CH_3$, and $-CH_2NHCOCH_2CH_3$;

xi) $-(CR^{102a}R^{102b})_aN(R^{101})\,C(O)_2R^{101}$; for example, $-NHCO_2CH_3$, $-CH_2NHCO_2CH_3$, $-NHCO_2CH_2CH_3$, and $-CH_2NHCO_2CH_2CH_3$;

xii) $-(CR^{102a}R^{102b})_aN(R^{101})_2$; for example, $-NH_2$, $-CH_2NH_2$, $-NHCH_3$, $-CH_2NHCH_3$, $-N(CH_3)_2$, and $-CH_2N(CH_3)_2$;

xiii) halogen; –F, –Cl, –Br, and –I;

xiv) $-(CR^{102a}R^{102b})_aCN$;

xv) $-(CR^{102a}R^{102b})_aNO_2$;

xvi) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, $j + k = 3$; the index j' is an integer from 0 to 2, $j' + k' = 2$; for example, $-CH_2F$, $-CHF_2$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;

xvii) $-(CR^{102a}R^{102b})_aSR^{101}$; $-SH$, $-CH_2SH$, $-SCH_3$, $-CH_2SCH_3$, $-SC_6H_5$, and $-CH_2SC_6H_5$;

xviii) $-(CR^{102a}R^{102b})_aSO_2R^{101}$; for example, $-SO_2H$, $-CH_2SO_2H$, $-SO_2CH_3$, $-CH_2SO_2CH_3$, $-SO_2C_6H_5$, and $-CH_2SO_2C_6H_5$; and

xix) $-(CR^{102a}R^{102b})_aSO_3R^{101}$; for example, $-SO_3H$, $-CH_2SO_3H$, $-SO_3CH_3$, $-CH_2SO_3CH_3$, $-SO_3C_6H_5$, and $-CH_2SO_3C_6H_5$;

wherein each R^{101} is independently hydrogen, substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, phenyl, benzyl, heterocyclic, or heteroaryl; or two R^{101} units can be taken together to form a ring comprising 3-7 atoms; R^{102a} and R^{102b} are each independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl; the index “a” is from 0 to 4.

The substitutions for hydrogen defined herein above, for example, substituted C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl, substituted C_6 or C_{10}

aryl, substituted C_7 or C_{11} alkylenearyl, substituted C_1-C_9 heterocyclic rings, substituted C_1-C_9 heteroaryl rings, and R^{101}, can be optionally substituted by one or more of the following substitutions for hydrogen:

i) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl; methyl (C_1), ethyl (C_2), ethenyl (C_2), ethynyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), 3-propenyl (C_3), 1-propenyl (*also* 2-methylethenyl) (C_3), isopropenyl (*also* 2-methylethen-2-yl) (C_3), prop-2-ynyl (*also* propargyl) (C_3), propyn-1-yl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), buten-4-yl (C_4), cyclopentyl (C_5), cyclohexyl (C_6);

ii) C_6 or C_{10} aryl; for example, phenyl, naphthyl (also referred to herein as naphthylen-1-yl (C_{10}) or naphthylen-2-yl (C_{10}));

iii) C_7 or C_{11} alkylenearyl; for example, benzyl, 2-phenylethyl, naphthylen-2-ylmethyl;

iv) C_1-C_9 heterocyclic rings; as described herein below;

v) C_1-C_9 heteroaryl rings; as described herein below;

vi) $-(CR^{202a}R^{202b})_bOR^{201}$; for example, $-OH$, $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_2CH_3$, $-OCH_2CH_2CH_3$, and $-CH_2OCH_2CH_2CH_3$;

vii) $-(CR^{202a}R^{202b})_bC(O)R^{201}$; for example, $-COCH_3$, $-CH_2COCH_3$, $-COCH_2CH_3$, $-CH_2COCH_2CH_3$, $-COCH_2CH_2CH_3$, and $-CH_2COCH_2CH_2CH_3$;

viii) $-(CR^{202a}R^{202b})_bC(O)OR^{201}$; for example, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CH_2CO_2CH_2CH_2CH_3$;

ix) $-(CR^{202a}R^{202b})_bC(O)N(R^{201})_2$; for example, $-CONH_2$, $-CH_2CONH_2$, $-CONHCH_3$, $-CH_2CONHCH_3$, $-CON(CH_3)_2$, and $-CH_2CON(CH_3)_2$;

x) $-(CR^{202a}R^{202b})_bN(R^{201})\,C(O)R^{201}$; for example, $-NHCOCH_3$, $-CH_2NHCOCH_3$, $-NHCOCH_2CH_3$, and $-CH_2NHCOCH_2CH_3$;

xi) $-(CR^{202a}R^{202b})_bN(R^{201})\,C(O)_2R^{201}$; for example, $-NHCO_2CH_3$, $-CH_2NHCO_2CH_3$, $-NHCO_2CH_2CH_3$, and $-CH_2NHCO_2CH_2CH_3$;

xii) $-(CR^{202a}R^{202b})_bN(R^{201})_2$; for example, $-NH_2$, $-CH_2NH_2$, $-NHCH_3$, $-CH_2NHCH_3$, $-N(CH_3)_2$, and $-CH_2N(CH_3)_2$;

xiii) halogen; $-F$, $-Cl$, $-Br$, and $-I$;

xiv) $-(CR^{202a}R^{202b})_bCN$;

xv) $-(CR^{202a}R^{202b})_bNO_2$;

xvi) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, j + k = 3; the index j' is an integer from 0 to 2, j' + k' = 2; for example, $-CH_2F$, $-CHF_2$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;

xvii) $-(CR^{202a}R^{202b})_bSR^{201}$; –SH, $-CH_2SH$, $-SCH_3$, $-CH_2SCH_3$, $-SC_6H_5$, and $-CH_2SC_6H_5$;

xviii) $-(CR^{202a}R^{202b})_bSO_2R^{201}$; for example, $-SO_2H$, $-CH_2SO_2H$, $-SO_2CH_3$, $-CH_2SO_2CH_3$, $-SO_2C_6H_5$, and $-CH_2SO_2C_6H_5$; and

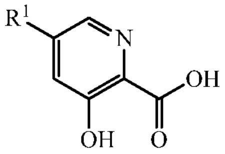
xix) $-(CR^{202a}R^{202b})_bSO_3R^{201}$; for example, $-SO_3H$, $-CH_2SO_3H$, $-SO_3CH_3$, $-CH_2SO_3CH_3$, $-SO_3C_6H_5$, and $-CH_2SO_3C_6H_5$;

wherein each R^{201} is independently hydrogen, C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, phenyl, benzyl, heterocyclic, or heteroaryl; or two R^{201} units can be taken together to form a ring comprising 3-7 atoms; R^{202a} and R^{202b} are each independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl; the index "b" is from 0 to 4.

For the purposes of the present disclosure the terms "compound," "analog," and "composition of matter" stand equally well for each other and are used interchangeably throughout the specification. The disclosed compounds include all enantiomeric forms, diastereomeric forms, salts, and the like.

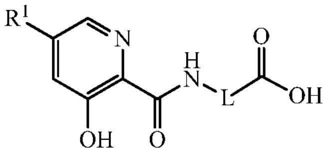
The compounds disclosed herein include all salt forms, for example, salts of both basic groups, *inter alia*, amines, as well as salts of acidic groups, *inter alia*, carboxylic acids. The following are non-limiting examples of anions that can form salts with protonated basic groups: chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, citrate, and the like. The following are non-limiting examples of cations that can form salts of acidic groups: ammonium, sodium, lithium, potassium, calcium, magnesium, bismuth, lysine, tromethamine, meglumine and the like.

The disclosed process can be used to prepare compounds having the formula:

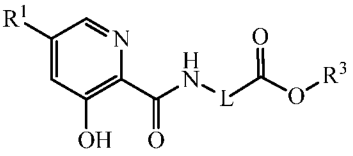


wherein R and R^1 are further defined herein.

Compounds having the formula:



wherein L is a linking group defined herein, have been found to exhibit prolyl hydroxylase inhibition (antagonism). Compounds of this formula have also been found to stabilize hypoxia inducible factor-2 alpha (HIF-2a). It has also been found that esters and amides having the formula:



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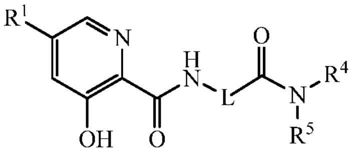
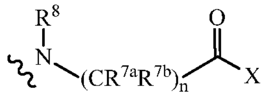


can hydrolyze *in vivo, in vitro* and *ex vivo* to the corresponding carboxylic acids shown above. As such, these esters and amides are referred to herein as “prodrugs.”

R Units

R units have the formula:



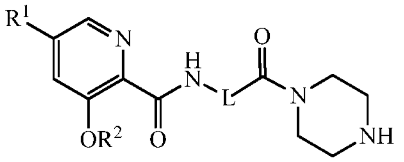
wherein X is chosen from:

i) –OH;
ii) $-OR^3$;
iii) $-NR^4R^5$; and
iv) $-OM^1$.

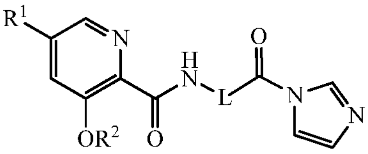
R^3 is C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl; C_2-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkenyl; or C_2-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkynyl, or benzyl.

R^4 and R^5 are each independently hydrogen, C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl; C_2-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkenyl; or C_2-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkynyl; benzyl; or R^4 and R^5 can be taken together with the nitrogen atom to form a 3 to 10 member ring, wherein the ring can optionally contain one or more heteroatoms chosen from oxygen (O), nitrogen (N), or sulfur (S). M^1 represents a cation as further described herein below.

When a ring is formed from R^4 and R^5 and the ring contains a ring nitrogen other than the nitrogen atom to which R^4 and R^5 are bonded, then the nitrogen atom can have the form –NR^9– or =N–, wherein R^9 can be hydrogen or methyl. Non-limiting examples of this embodiment includes compounds having the formula:



and



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In one aspect, X is hydroxyl, –OH.

In a further aspect, X is –OR^3. One embodiment of this aspect relates to X units wherein R^3 is C_1-C_6 linear alkyl, for example, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (C_5), and n-hexyl (C_6). Non-limiting examples include the methyl ester, the ethyl ester, the n-propyl ester, and the like.

Another embodiment of this aspect relates to X units wherein R^3 is C_3-C_6 branched alkyl non-limiting examples of which include *iso*-propyl (C_3), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), 1-methylbutyl (C_5), 2-methylbutyl (C_5), 3-methylbutyl (C_5), and 4-methylpentyl (C_6).

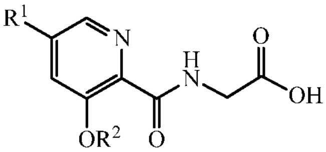
A further embodiment of this aspect relates to X units wherein R^3 is C_3-C_6 cyclic alkyl, for example, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), and cyclohexyl (C_6).

In another aspect, X is –NR^4R^5. One embodiment of this aspect relates to X units wherein R^4 and R^5 are both hydrogen; –NH_2.

A further embodiment of this aspect relates to X units wherein R^4 and R^5 are independently chosen from hydrogen, C_1-C_4 linear alkyl, C_3-C_4 branched alkyl, or C_3-C_4 cyclic alkyl, for example, methyl (C_1), ethyl (C_2), n-propyl (C_3), iso-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), and *tert*-butyl (C_4). Non-limiting examples of this embodiment include –NH_2, –$NHCH_3$, –$N(CH_3)_2$, –NHC_2H_5, –$N(C_2H_5)_2$, and –$N(CH_3)(C_2H_5)$.

L is a linking unit having the formula –$(CR^{7a}R^{7b})_n$– wherein R^{7a} and R^{7b} can be independently chosen from hydrogen, C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl. The index n is an integer from 1 to 4.

In one aspect of L units, R^{7a} and R^{7b} are both hydrogen and the index n is an integer from 1 to 4, *i.e.*, –CH_2– (methylene), –CH_2CH_2– (ethylene), –$CH_2CH_2CH_2$– (propylene), and $-CH_2CH_2CH_2CH_2-$ (butylene). One iteration of L units according to this aspect relates to compounds having the formula:



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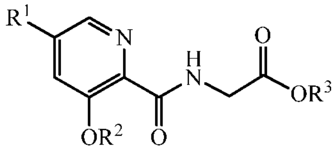

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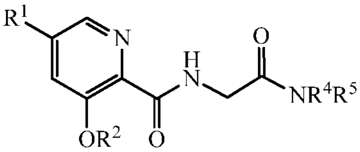

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A further aspect of L units relates to L units wherein R^{7a} and R^{7b} are independently chosen from hydrogen, methyl (C_1), ethyl (C_2), n-propyl (C_3), and *iso*-propyl (C_3) and the index n is an integer from 1 to 4. One embodiment of this aspect relates to L units wherein R^{7a} is hydrogen and R^{7b} is chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), and *iso*-propyl (C_3), and the index n is an integer from 1 or 3. Non-limiting examples of this embodiment includes $-CH(CH_3)-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH(CH_3)-$.

A yet further aspect of L units relates to L units wherein R^{7a} and R^{7b} are independently chosen from methyl (C_1), ethyl (C_2), n-propyl (C_3), and *iso*-propyl (C_3) and the index n is an integer from 1 to 4. A non-limiting example of this aspect has the formula $-C(CH_3)_2-$.

In a still further aspect of L units, L units can be derived from the reaction of an amino acid with a 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine as described herein below in the disclosure of process step D. One embodiment of this aspect of L relates to L units wherein R^{7b} is hydrogen and R^{7a} is chosen from hydrogen, methyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, hydroxymethyl, 1-hydroxyethyl, thiomethyl, 2-(methylthio)ethyl, benzyl, (4-hydroxyphenyl)methyl, indol-3-ylmethyl, imidazol-4-ylmethyl, 3-gunidinylpropyl, 4-aminobutyl, carboxymethyl, 2-carboxyethyl, acetamide, or R^8 and R^{7a} can be taken together to form a pyrrolidinyl ring, for example, when proline is reacted with the 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine.

The index n can be any integer from 1 to 4, for example n can equal 1, n can equal 2, n can equal 3, and n can equal 4.

R^8 is hydrogen, methyl (C_1) or ethyl (C_2). In one aspect R^8 is hydrogen. In a further aspect R^8 is methyl (C_1). In another aspect R^8 is ethyl (C_2).

R^1 Units

R^1 units are chosen from:

i) substituted or unsubstituted C_6 or C_{10} aryl; and

ii) substituted or unsubstituted C_1-C_9 heteroaryl.

Non-limiting examples of substitutions for a hydrogen atom on R^1 units, or alternatively an R^{10} unit when R^1 is represented by an A ring, include:

- i) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl; for example, methyl (C_1), ethyl (C_2), ethenyl (C_2), ethynyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), 3-propenyl (C_3), 1-propenyl (*also* 2-methylethenyl) (C_3), isopropenyl (*also* 2-methylethen-2-yl) (C_3), prop-2-ynyl (*also* propargyl) (C_3), propyn-1-yl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), buten-4-yl (C_4), cyclopentyl (C_5), cyclohexyl (C_6);
- ii) C_6 or C_{10} aryl; for example, phenyl, naphthyl (also referred to herein as naphthylen-1-yl (C_{10}) or naphthylen-2-yl (C_{10}));
- iii) C_7 or C_{11} alkylenearyl; for example, benzyl, 2-phenylethyl, naphthylen-2-ylmethyl;
- iv) C_1-C_9 heterocyclic rings; as described herein below;
- v) C_1-C_9 heteroaryl rings; as described herein below;
- vi) $-(CR^{102a}R^{102b})_aOR^{101}$; for example, $-OH$, $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_2CH_3$, $-OCH_2CH_2CH_3$, and $-CH_2OCH_2CH_2CH_3$;
- vii) $-(CR^{102a}R^{102b})_aC(O)R^{101}$; for example, $-COCH_3$, $-CH_2COCH_3$, $-COCH_2CH_3$, $-CH_2COCH_2CH_3$, $-COCH_2CH_2CH_3$, and $-CH_2COCH_2CH_2CH_3$;
- viii) $-(CR^{102a}R^{102b})_aC(O)OR^{101}$; for example, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CH_2CO_2CH_2CH_2CH_3$;
- ix) $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$; for example, $-CONH_2$, $-CH_2CONH_2$, $-CONHCH_3$, $-CH_2CONHCH_3$, $-CON(CH_3)_2$, and $-CH_2CON(CH_3)_2$;
- x) $-(CR^{102a}R^{102b})_aN(R^{101})C(O)R^{101}$; for example, $-NHCOCH_3$, $-CH_2NHCOCH_3$, $-NHCOCH_2CH_3$, and $-CH_2NHCOCH_2CH_3$;
- xi) $-(CR^{102a}R^{102b})_aN(R^{101})C(O)_2R^{101}$; for example, $-NHCO_2CH_3$, $-CH_2NHCO_2CH_3$, $-NHCO_2CH_2CH_3$, and $-CH_2NHCO_2CH_2CH_3$;
- xii) $-(CR^{102a}R^{102b})_aN(R^{101})_2$; for example, $-NH_2$, $-CH_2NH_2$, $-NHCH_3$, $-CH_2NHCH_3$, $-N(CH_3)_2$, and $-CH_2N(CH_3)_2$;
- xiii) halogen; –F, –Cl, –Br, and –I;
- xiv) $-(CR^{102a}R^{102b})_aCN$;

xv) $-(CR^{102a}R^{102b})_aNO_2$;

xvi) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, j + k = 3; the index j' is an integer from 0 to 2, j' + k' = 2; for example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;

xvii) $-(CR^{102a}R^{102b})_aSR^{101}$; $-SH$, $-CH_2SH$, $-SCH_3$, $-CH_2SCH_3$, $-SC_6H_5$, and $-CH_2SC_6H_5$;

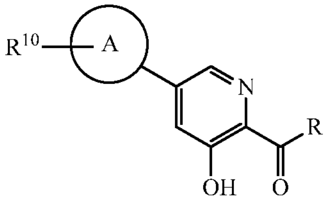
xviii) $-(CR^{102a}R^{102b})_aSO_2R^{101}$; for example, $-SO_2H$, $-CH_2SO_2H$, $-SO_2CH_3$, $-CH_2SO_2CH_3$, $-SO_2C_6H_5$, and $-CH_2SO_2C_6H_5$; and

xix) $-(CR^{102a}R^{102b})_aSO_3R^{101}$; for example, $-SO_3H$, $-CH_2SO_3H$, $-SO_3CH_3$, $-CH_2SO_3CH_3$, $-SO_3C_6H_5$, and $-CH_2SO_3C_6H_5$; or

xx) two substitutions for hydrogen can be taken together to form a substituted or unsubstituted C_2-C_8 heterocyclic ring, wherein the ring substitution can be one or more of the substitutions defined in (i) to (xix) herein above and the ring can comprise one or more heteroatoms chosen from oxygen (O) sulfur (S), or nitrogen (N);

wherein each R^{101} is independently hydrogen, substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, phenyl, benzyl, heterocyclic, or heteroaryl; or two R^{101} units can be taken together to form a ring comprising 3-7 atoms; R^{102a} and R^{102b} are each independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl; the index "a" is from 0 to 4.

Stated in another way, the disclosed process relates to the formation of compounds having the formula:



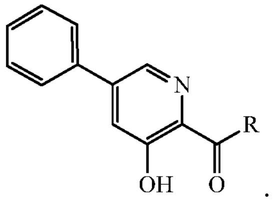
wherein the A ring represents R^1 units wherein R^1 can be:

i) substituted or unsubstituted C_6 or C_{10} aryl; and

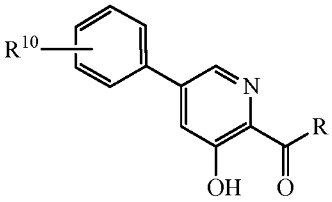
ii) substituted or unsubstituted C_1-C_9 heteroaryl;

wherein the substitutes for hydrogen atoms on the A ring are one or more R^{10} units that are independently chosen and further described herein.

One aspect of R^1 relates to substituted or unsubstituted C_6 aryl, *i.e.*, substituted or unsubstituted phenyl. A first embodiment of this aspect relates to R^1 equal to phenyl, for example, compounds having the formula:



A further aspect of R^1 relates to R^1 units that are substituted phenyl having the formula:



wherein R^{10} represents from 1 to 5 independently chosen substitutions for hydrogen; or two R^{10} units can be taken together to form a substituted or unsubstituted C_4-C_8 cycloalkyl ring, a substituted or unsubstituted C_6 aryl ring (phenyl), a substituted or unsubstituted C_2-C_8 heterocyclic ring, or a substituted or unsubstituted C_3 to C_5 heteroaryl ring, wherein the heterocyclic and heteroaryl rings comprise one or more hetero atoms independently chosen from oxygen (O), nitrogen (N), or sulfur (S).

One embodiment of this aspect of R^1 units relates to compounds comprising substitutions on R^1 of one or more units independently chosen from:

i) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl;
ii) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkoxy; and
iii) halogen: –F, –Cl, –Br, and –I.

One iteration of this embodiment relates to compounds comprising one or more R^{10} units that are halogen, thereby forming the following non-limiting examples of R^1 units: 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 3,5-dichlorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,3,6-trichlorophenyl, 2,4,5-trichlorophenyl, 3,4,5-trichlorophenyl, and 2,4,6-trichlorophenyl.

A further iteration relates to compounds comprising one or more R^{10} units that are C_1-C_4 linear, C_3-C_4 branched or C_3-C_4 cyclic alkyl, thereby forming the following non-limiting examples of R^1 units: 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 2,3,4-trimethylphenyl, 2,3,5-trimethylphenyl, 2,3,6-trimethylphenyl, 2,4,5-trimethylphenyl, 2,4,6-trimethylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2,3-diethylphenyl, 2,4-diethylphenyl, 2,5-diethylphenyl, 2,6-diethylphenyl, 3,4-diethylphenyl, 2,3,4-triethylphenyl, 2,3,5-triethylphenyl, 2,3,6-triethylphenyl, 2,4,5-triethylphenyl, 2,4,6-triethylphenyl, 2-isopropylphenyl, 3-isopropylphenyl, and 4-isopropylphenyl.

Another iteration relates to compounds comprising one or more R^{10} units that are C_1-C_4 linear, C_3-C_4 branched or C_3-C_4 cyclic alkoxy, thereby forming the following non-limiting examples of R^1 units: 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2,3,5-trimethoxyphenyl, 2,3,6-trimethoxyphenyl, 2,4,5-trimethoxyphenyl, 2,4,6-trimethoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2,3-diethoxyphenyl, 2,4-diethoxyphenyl, 2,5-diethoxyphenyl, 2,6-diethoxyphenyl, 3,4-diethoxyphenyl, 2,3,4-triethoxyphenyl, 2,3,5-triethoxyphenyl, 2,3,6-triethoxyphenyl, 2,4,5-triethoxyphenyl, 2,4,6-triethoxyphenyl, 2-isopropoxyphenyl, 3-isopropoxyphenyl, and 4-isopropoxyphenyl.

A yet still further iteration relates to compounds comprising one or more R^{10} units that comprise at least one of each substitution chosen from C_1-C_4 linear or halogen, thereby forming the following non-limiting examples of R^1 units: 2-chloro-3-methylphenyl, 2-chloro-4-methylphenyl, 2-chloro-5-methylphenyl, 2-chloro-6-methylphenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 3-chloro-5-methylphenyl, 3-chloro-6-methyl-phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluoro-5-methylphenyl, 2-fluoro-6-methylphenyl, 3-fluoro-2-methylphenyl, 3-fluoro-4-methylphenyl, 3-fluoro-5-methylphenyl, and 3-fluoro-6-methylphenyl.

One embodiment of this aspect of R^1 units relates to compounds comprising one or more R^{10} units independently chosen from:

i) $-(CR^{102a}R^{102b})_aCN$;

ii) $-(CR^{102a}R^{102b})_aNO_2$; and

iii) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, $j + k = 3$; the index j' is an integer from 0 to 2, $j' + k' = 2$.

On iteration of this embodiment relates to compounds comprising one or more R^{10} units that are $–(CH_2)_aCN$, wherein the index a is 0 or 1, thereby forming the following non-limiting examples of R^1 units: 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-(cyanomethyl)phenyl, 3-(cyanomethyl)phenyl, 4-(cyanomethyl)phenyl, 2,3-dicyanophenyl, 3,4-dicyanophenyl, and 3,5-dicyanophenyl.

Another iteration of this embodiment relates to compounds comprising one or more R^{10} units that are $–(CH_2)_aNO_2$, wherein the index a is 0 or 1, thereby forming the following non-limiting examples of R^1 units: 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-(nitromethyl)phenyl, 3-(nitromethyl)phenyl, 4-(nitromethyl)phenyl, 2,3-dinitrophenyl, 3,4-dinitrophenyl, and 3,5-dinitrophenyl.

A further iteration of this embodiment relates to compounds comprising one or more R^{10} units that are $–CH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, j + k = 3, wherein the index a is 0 or 1, thereby forming the following non-limiting examples of R^1 units: $–CH_2F$, $–CH_2CH_2F$, $–CHF_2$, $–CH_2CHF_2$, $–CF_3$, $–CH_2CF_3$, $–CHFCH_2F$, $–CF_2CHF_2$, $–CF_2CF_3$, $–CH_2Cl$, $–CH_2CH_2Cl$, $–CHCl_2$, $–CH_2CHCl_2$, $–CCl_3$, $–CH_2CCl_3$, $–CHClCH_2Cl$, $–CCl_2CHCl_2$, and $–CCl_2CCl_3$.

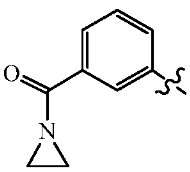
One embodiment of this aspect of R^1 units relates to compounds comprising one or more R^{10} units independently chosen from:

i) $–(CR^{102a}R^{102b})_aN(R^{101})_2$;
ii) $–(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$; and
iii) $–(CR^{102a}R^{102b})_aN(R^{101})C(O)_2R^{101}$.

One iteration of this embodiment relates to compounds comprising one or more R^{10} units that are $–(CR^{102a}R^{102b})_aN(R^{101})_2$, wherein the index a is 0 or 1, thereby forming the following non-limiting examples of R^1 units: 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2,3-diaminophenyl, 3,4-diaminophenyl, 3,5-diaminophenyl, 2-methylaminophenyl, 3-methylaminophenyl, 4-methylaminophenyl, 2,3-(dimethylamino)phenyl, 3,4-(dimethylamino)phenyl, 3,5-(dimethylamino)phenyl, 2,3,4-triaminophenyl, 2,3,5-triaminophenyl, 2,3,6-triaminophenyl, 2,4,5-triaminophenyl, 2,4,6-triaminophenyl, 2,4-(dimethylamino)phenyl, 2,5-(dimethylamino)phenyl, 2,6-(dimethylamino)phenyl, 3,4-(dimethylamino)phenyl, 2,3,4-(dimethylamino)phenyl, 2,3,5-(dimethylamino)phenyl, 2,3,6-(dimethylamino)phenyl, 2,4,5-(dimethylamino)phenyl, 3,4,5-(dimethylamino)phenyl, and 2,4,6-(dimethylamino)phenyl.

Another iteration of this embodiment relates to compounds comprising one or more R^{10} units that are $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$, wherein R^{101} is chosen from hydrogen, C_1-C_6 linear, C_3-C_6 branched alkyl or C_3-C_6 cyclic alkyl, and the index a is 0 or 1, thereby forming the following non-limiting examples of R^1 units: $-C(O)NH_2$, $-C(O)NHCH_3$, $-CH_2C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-CH_2C(O)N(CH_3)_2$, $-C(O)NHCH_2CH_3$, $-CH_2C(O)NHCH_2CH_3$, $-C(O)N(CH_2CH_3)_2$, $-CH_2C(O)N(CH_2CH_3)_2$, $-C(O)NHCH(CH_3)_2$, $-CH_2C(O)NHCH(CH_3)_2$, $-C(O)N[CH(CH_3)_2]_2$, and $-CH_2C(O)N[CH(CH_3)_2]_2$.

Another iteration of this embodiment relates to compounds comprising one or more R^{10} units that are $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$, wherein two R^{101} units are taken together to form a ring having from 3 to 7 atoms and the index a is 0 or 1, thereby forming R^1 units having, for example, the formulae:



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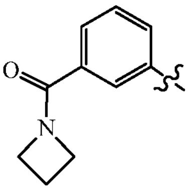

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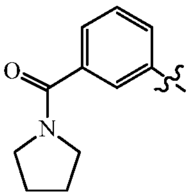

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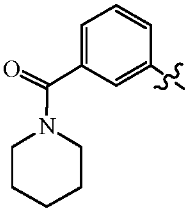

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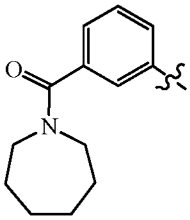

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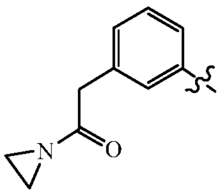

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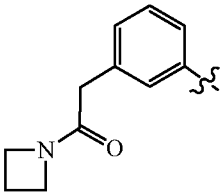

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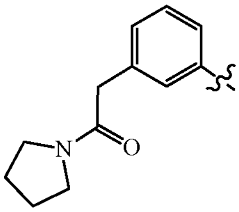

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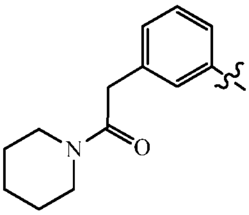

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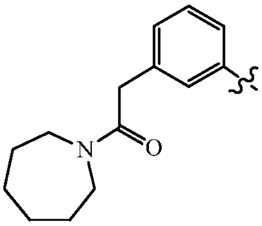
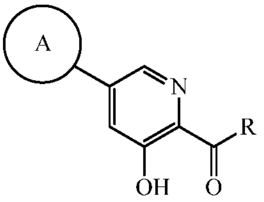


.

A further iteration of this embodiment relates to compounds comprising one or more R^{10} units that are $-(CR^{102a}R^{102b})_aN(R^{101})C(O)_2R^{101}$; wherein R^{101} is chosen from hydrogen, C_1-C_6 linear, C_3-C_6 branched alkyl or C_3-C_6 cyclic alkyl, and the index a is 0 or 1, thereby forming the following non-limiting examples of R^1 units: $-NHC(O)CH_3$, $-CH_2NHC(O)CH_3$, $-NHC(O)CH_2CH_3$, $-CH_2NHC(O)CH_2CH_3$, $-NHC(O)CH_2CH_2CH_3$, $-CH_2NHC(O)CH_2CH_2CH_3$, $-NHC(O)$(cyclopropyl), and $-CH_2NHC(O)$(cyclopropyl).

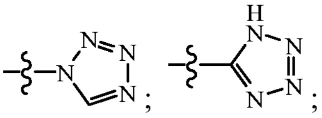
Another aspect of R^1 relates to R^1 units that are substituted or unsubstituted C_1-C_9 heteroaryl. One embodiment of this aspect relates to R^1 equal to C_1-C_9 heteroaryl, for example, compounds having the formula:



wherein ring A represent a C_1-C_9 heteroaryl unit non-limiting examples of which include: 1,2,3,4-tetrazolyl (C_1), [1,2,3]triazolyl (C_2), [1,2,4]triazolyl (C_2), [1,2,4]oxadiazolyl (C_2), [1,3,4]oxadiazolyl (C_2), [1,2,4]thiadiazolyl (C_2), [1,3,4]thiadiazolyl (C_2), isothiazolyl (C_3), thiazolyl (C_3), imidazolyl (C_3), oxazolyl (C_3), isoxazolyl (C_3), pyrazolyl (C_3), pyrrolyl (C_4), furanyl (C_4), thiophenyl (C_4), triazinyl (C_3), pyrimidinyl (C_4), pyrazinyl (C_4), pyridazinyl (C_4), pyridinyl (C_5), purinyl (C_5), xanthinyl (C_5), hypoxanthinyl (C_5), benzimidazolyl (C_7), indolyl (C_8), quinazolinyl (C_8), quinolinyl (C_9), and isoquinolinyl (C_9).

In a further embodiment of this aspect the C_1-C_9 heteroaryl unit can be bonded to the core pyridine ring at any suitable position, non-limiting examples of which include:

i)



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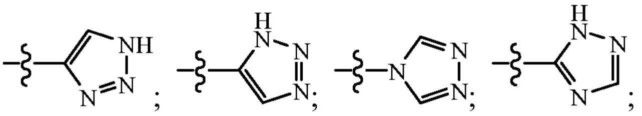

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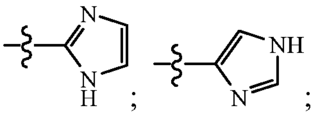

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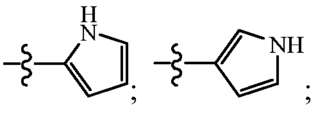

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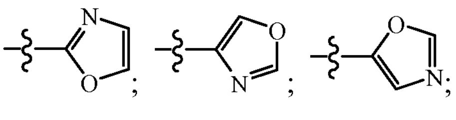

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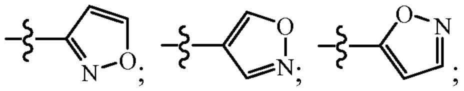

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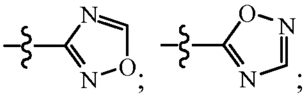

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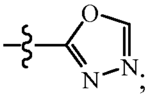

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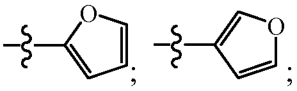

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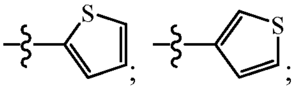

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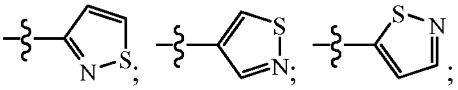

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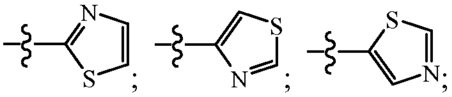

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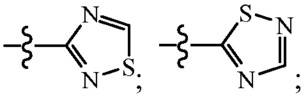

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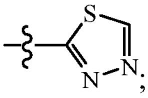

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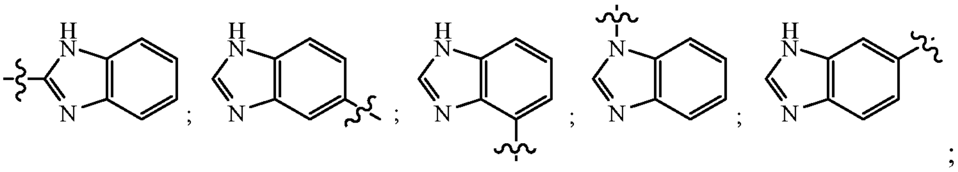

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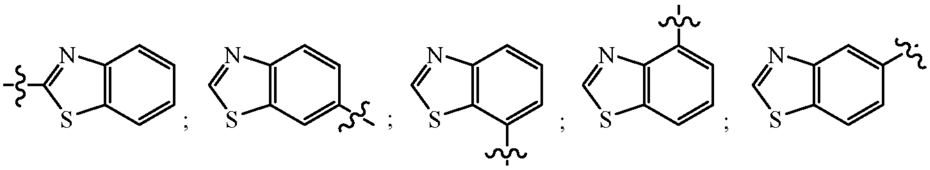
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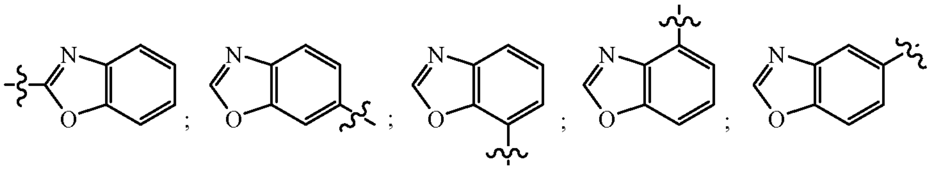
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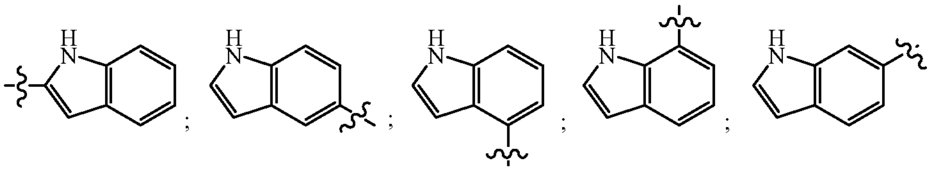
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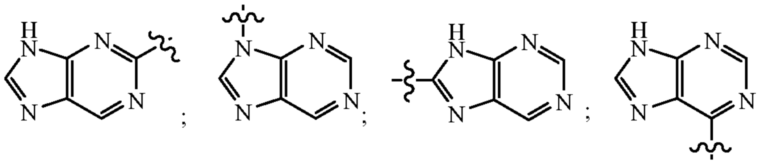

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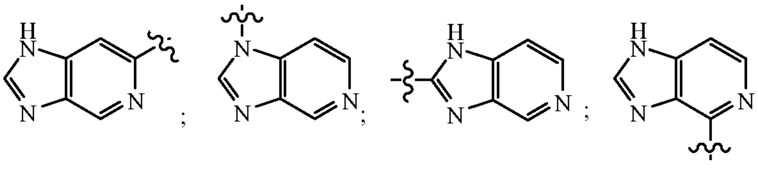
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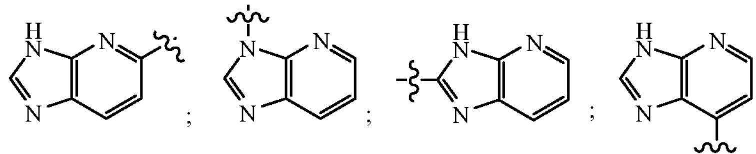
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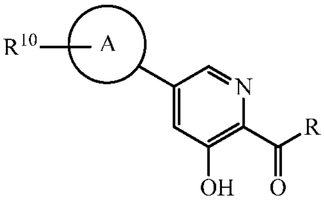
Another embodiment of this aspect relates to R^1 units equal to substituted C_1-C_9 heteroaryl, for example, compounds having the formula:



wherein ring A represent a C_1-C_9 heteroaryl unit non-limiting examples of which include: 1,2,3,4-tetrazolyl (C_1), [1,2,3]triazolyl (C_2), [1,2,4]triazolyl (C_2), [1,2,4]oxadiazolyl (C_2), [1,3,4]oxadiazolyl (C_2), [1,2,4]thiadiazolyl (C_2), [1,3,4]thiadiazolyl (C_2), isothiazolyl (C_3), thiazolyl (C_3), imidazolyl (C_3), oxazolyl (C_3), isoxazolyl (C_3), pyrazolyl (C_3), pyrrolyl (C_4), furanyl (C_4), thiophenyl (C_4), triazinyl (C_3), pyrimidinyl (C_4), pyrazinyl (C_4), pyridazinyl (C_4), pyridinyl (C_5), purinyl (C_5), xanthinyl (C_5), hypoxanthinyl (C_5), benzimidazolyl (C_7), indolyl (C_8), quinazolinyl (C_8), quinolinyl (C_9), and isoquinolinyl (C_9).

Non-limiting examples of substitutions for a hydrogen atom on R^1 C_1-C_9 heteroaryl units include:

i) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl; methyl (C_1), ethyl (C_2), ethenyl (C_2), ethynyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), 3-propenyl (C_3), 1-propenyl (*also* 2-methylethenyl) (C_3), isopropenyl (*also* 2-methylethen-2-yl) (C_3), prop-2-ynyl (*also* propargyl) (C_3), propyn-1-yl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), buten-4-yl (C_4), cyclopentyl (C_5), cyclohexyl (C_6);

ii) C_6 or C_{10} aryl; for example, phenyl, naphthyl (also referred to herein as naphthylen-1-yl (C_{10}) or naphthylen-2-yl (C_{10}));

iii) C_7 or C_{11} alkylenearyl; for example, benzyl, 2-phenylethyl, naphthylen-2-ylmethyl;

iv) C_1-C_9 heterocyclic rings; as described herein below;

v) C_1-C_9 heteroaryl rings; as described herein below;

vi) $-(CR^{102a}R^{102b})_aOR^{101}$; for example, $-OH$, $-CH_2OH$, $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_2CH_3$, $-OCH_2CH_2CH_3$, and $-CH_2OCH_2CH_2CH_3$;

vii) $-(CR^{102a}R^{102b})_aC(O)R^{101}$; for example, $-COCH_3$, $-CH_2COCH_3$, $-COCH_2CH_3$, $-CH_2COCH_2CH_3$, $-COCH_2CH_2CH_3$, and $-CH_2COCH_2CH_2CH_3$;

viii) $-(CR^{102a}R^{102b})_aC(O)OR^{101}$; for example, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CH_2CO_2CH_2CH_2CH_3$;

ix) $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$; for example, $-CONH_2$, $-CH_2CONH_2$, $-CONHCH_3$, $-CH_2CONHCH_3$, $-CON(CH_3)_2$, and $-CH_2CON(CH_3)_2$;

x) $-(CR^{102a}R^{102b})_aN(R^{101})C(O)R^{101}$; for example, $-NHCOCH_3$, $-CH_2NHCOCH_3$, $-NHCOCH_2CH_3$, and $-CH_2NHCOCH_2CH_3$;

xi) $-(CR^{102a}R^{102b})_aN(R^{101})C(O)_2R^{101}$; for example, $-NHCO_2CH_3$, $-CH_2NHCO_2CH_3$, $-NHCO_2CH_2CH_3$, and $-CH_2NHCO_2CH_2CH_3$;

xii) $-(CR^{102a}R^{102b})_aN(R^{101})_2$; for example, $-NH_2$, $-CH_2NH_2$, $-NHCH_3$, $-CH_2NHCH_3$, $-N(CH_3)_2$, and $-CH_2N(CH_3)_2$;

xiii) halogen; –F, –Cl, –Br, and –I;

xiv) $-(CR^{102a}R^{102b})_aCN$;

xv) $-(CR^{102a}R^{102b})_aNO_2$;

xvi) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, $j + k = 3$; the index j' is an integer from 0 to 2, $j' + k' = 2$; for example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;

xvii) $-(CR^{102a}R^{102b})_aSR^{101}$; $-SH$, $-CH_2SH$, $-SCH_3$, $-CH_2SCH_3$, $-SC_6H_5$, and $-CH_2SC_6H_5$;

xviii) $-(CR^{102a}R^{102b})_aSO_2R^{101}$; for example, $-SO_2H$, $-CH_2SO_2H$, $-SO_2CH_3$, $-CH_2SO_2CH_3$, $-SO_2C_6H_5$, and $-CH_2SO_2C_6H_5$; and

xix) $-(CR^{102a}R^{102b})_aSO_3R^{101}$; for example, $-SO_3H$, $-CH_2SO_3H$, $-SO_3CH_3$, $-CH_2SO_3CH_3$, $-SO_3C_6H_5$, and $-CH_2SO_3C_6H_5$;

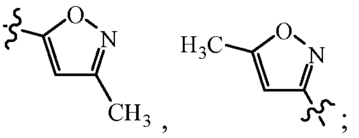
wherein each R^{101} is independently hydrogen, substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, phenyl, benzyl, heterocyclic, or heteroaryl; or two R^{101} units can be taken together to form a ring comprising 3-7 atoms; R^{102a} and R^{102b} are each independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl; the index "a" is from 0 to 4.

Non-limiting examples of substituted C_5-C_9 R^1 heteroaryl units include 2-methylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-(n-propyl)thiazol-4-yl, 2-(*iso*-propyl)thiazol-4-yl, 4,5-dimethylthiazol-2-yl, 4-ethyl-5-methylthiazol-2-yl, 4-methyl-5-ethylthiazol-2-yl, 4,5-diethylthiazol-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 4,5-dimethylimidazol-2-yl, 4-ethyl-5-methylimidazol-2-yl, 4-methyl-5-ethylimidazol-2-yl, 4,5-diethylimidazol-2-yl, 2,5-dimethylthiazol-4-yl, 2,4-dimethylthiazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 4,5-dimethyloxazol-2-yl, 4-ethyl-5-methyloxazol-2-yl, 4-methyl-5-ethyloxazol-2-yl, 4,5-diethyloxazol-2-yl, 2-methyloxazol-4-yl, 2-ethyloxazol-4-yl, 2-(n-propyl)oxazol-4-yl, 2-(*iso*-propyl)oxazol-4-yl, 2-methyloxazol-4-yl, 2-ethyloxazol-4-yl, 2-(n-propyl)oxazol-4-yl, 2-(*iso*-propyl)oxazol-4-yl, 5-methyl[1,2,4]oxadiazol-3-yl, 5-ethyl[1,2,4]-oxadiazol-3-yl, 5-

propyl[1,2,4]oxadiazol-3-yl, 5-cyclopropyl[1,2,4]oxadiazol-3-yl, 3-methyl[1,2,4]oxadiazol-5-yl, 3-ethyl[1,2,4]oxadiazol-5-yl, 3-(n-propyl)[1,2,4]oxadiazol-5-yl, 3-(*iso*-propyl)[1,2,4]oxadiazol-5-yl, 2,5-dimethylthiazol-4-yl, 2,4-dimethylthiazol-5-yl, 4-ethylthiazol-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 4,5-dimethylpyrimidin-2-yl, 4,5-diethylpyrimidin-2-yl, 4-methyl-5-ethyl-pyrimidin-2-yl, 4-ethyl-5-methyl-pyrimidin-2-yl, 4-(thiophen-2-yl)pyrimidin-2-yl, 5-(thiophen-2-yl)pyrimidin-2-yl, 4-(thiophen-3-yl)pyrimidin-2-yl, and 5-(thiophen-2-yl)pyrimidin-3-yl.

Non-limiting examples of substituted C_2-C_4 5-member heteroaryl rings include:

i)



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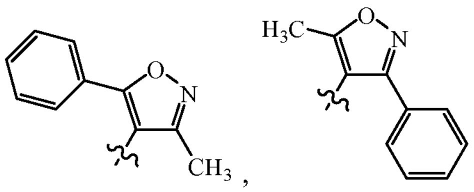

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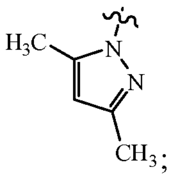

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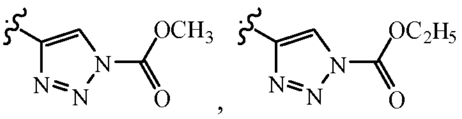

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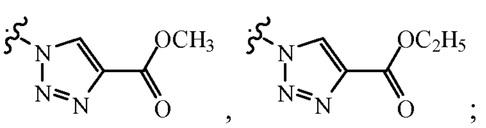

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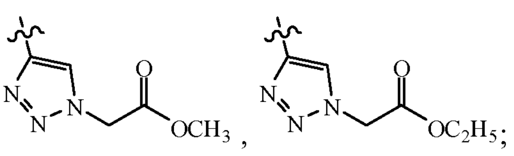
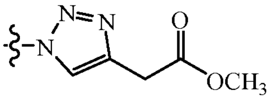


vii)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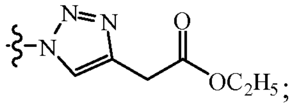
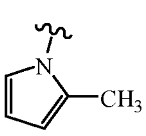

; and

viii)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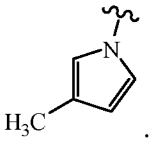
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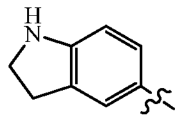
A yet further aspect of R^1 units relates to rings comprising two R^{10} substitutions for hydrogen that are taken together to form a substituted or unsubstituted C_2-C_8 heterocyclic ring. One embodiment of this aspect relates to R^1 units wherein two R^{10} units are taken together to form a substituted or unsubstituted C_7-C_9 heterocyclic R^1 ring system wherein the heterocyclic ring formed by the two R^{10} substitutions contains one or more nitrogen atoms. Non-limiting iterations of this embodiment include R^1 units having the formulae: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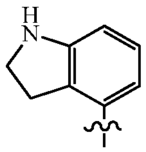
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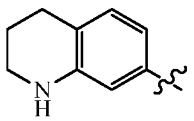
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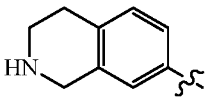
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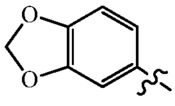
Another embodiment of this aspect relates to R^1 units wherein two R^{10} units are taken together to form a substituted or unsubstituted C_7-C_9 heterocyclic R^1 ring system wherein the heterocyclic ring formed by the two R^{10} substitutions contains one or more oxygen atoms. Non-limiting iterations of this embodiment include R^1 units having the formulae: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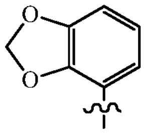
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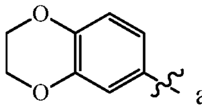
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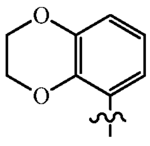
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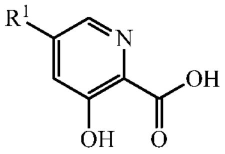
R^2 Units

R^2 units are chosen from C_1-C_{12} linear alkyl or C_3-C_{12} branched alkyl. In one embodiment R^2 can represent hydrogen. In another embodiment, R^2 is C_1-C_4 linear alkyl. Non-limiting examples include methyl, ethyl and n-propyl. In one example, R^2 is methyl. R^2 units relate to the alkoxide unit having the formula:

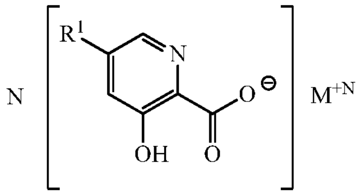
$$^{\ominus}OR^2$$

that is used in the process disclosed herein. As it relates to the alkoxide, the alkoxide can be derived from any suitable source, i.e., sodium methoxide, lithium ethoxide, and the like which the formulator can choose.

A further aspect of the present disclosure relates to a process for preparing intermediates having the formula:

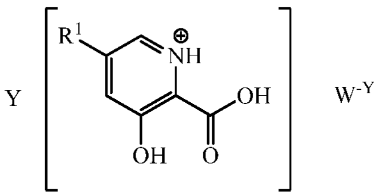


wherein $R^1$is the same as defined herein above. This aspect also includes salts of acids, for example, compounds having the formula:



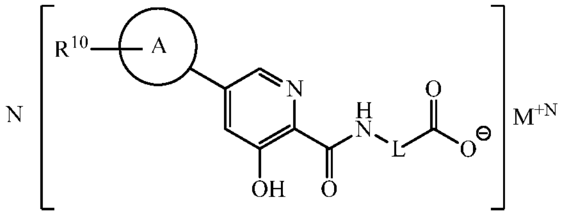
wherein M is a salt forming cation and N represents the cationic charge on M and the number of corresponding anionic units of the disclosed intermediates. The M units can comprise in one embodiment inorganic cations, *inter alia*, ammonium, sodium, lithium, potassium, calcium, magnesium, bismuth, and the like. In another embodiment, M units can comprise organic cation forming units, *inter alia*, lysine, ornithine, glycine, alanine, or other amino acids, basic organic compounds, *inter alia*, methylamine, dimethylamine, trimethylamine, and the like.

Another aspect of the present disclosure relates to a process for preparing intermediates having the formula:



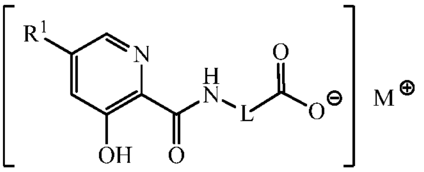
wherein W is a salt forming anion and Y represents the anionic charge on W and the number of corresponding number of the disclosed intermediates in this salt form. The W units can comprise in one embodiment inorganic anions, *inter alia*, chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, and the like. In another embodiment, W units can comprise organic anion forming units, *inter alia*, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, citrate, and the like.

In one aspect, the disclosed prolyl hydroxylase inhibitors can be isolated as a pharmaceutically acceptable salt having the formula:



wherein M is a salt forming cation and N represents the cationic charge on M and the number of corresponding anionic units present in the salt.

One aspect of the disclosed salts relates to prolyl hydroxylase inhibitors in the form of the mono-valent salt having the formula:



wherein M represents an inorganic or organic cation. Non-limiting examples of mono-valent cations include sodium, lithium, potassium, ammonium, silver, organic cations having the formula $HN^+R^aR^bR^c$ wherein R^a, R^b and R^c are each independently:

i) hydrogen;

ii) substituted or unsubstituted C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl;

iii) substituted or unsubstituted benzyl;

wherein one or more of R^a, R^b and R^c can be independently substituted by one or more units chosen from:

i) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkoxy;

ii) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic haloalkoxy;

iii) halogen;

iv) hydroxyl;

v) thio; or

vi) one or more of R^a, R^b and R^c can contain one or more units capable of forming a cation, anion, or zwitterions.

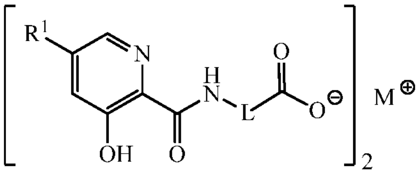
One iteration of this embodiment relates to cations wherein each of R^a, R^b and R^c are hydrogen or C_1-C_{12} linear alkyl. Non-limiting examples include methyl ammonium $[HN^+H_2(CH_3)]$, dimethyl ammonium $[HN^+H(CH_3)_2]$, trimethyl ammonium $[HN^+(CH_3)_3]$, ethyl ammonium $[HN^+H_2(CH_2CH_3)]$, diethyl ammonium $[HN^+H(CH_2CH_3)_2]$, triethyl ammonium $[HN^+(CH_2CH_3)_3]$, dimethylethyl ammonium $[HN^+(CH_3)_2(CH_2CH_3)]$, and methyldiethyl ammonium $[HN^+(CH_3)(CH_2CH_3)_2]$.

Another iteration of this embodiment relates to cations wherein one or more of R^a, R^b and R^c are chosen from hydrogen, unsubstituted C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl or substituted C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl. One embodiment relates to organic cations having one or more C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl chains substituted with hydroxy. Non-limiting examples include 2-hydroxyethyl ammonium (cation of monoethanolamine, cholinate) $[HN^+H_2(CH_2CH_2OH)]$, methyl-2-hydroxyethyl ammonium $[H_2N^+(CH_3)(CH_2CH_2OH)]$, di(2-hydroxyethyl) ammonium $[H_2N^+(CH_2CH_2OH)_2]$, tri(2-hydroxyethyl) ammonium $[HN^+(CH_2CH_2OH)_3]$, and tris(hydroxymethyl)methyl ammonium (cation of tris(hydroxymethyl)aminomethane) $[H_3N^+C[(CH_2OH)]_3]$. Also included are cations formed from amino sugars, for example, amino sugars having the formula $H_2N^+(CH_3)[(CHOH)_nCH_2OH]$ wherein n is from 1 to 7. A non-limiting example of an amino sugar suitable for forming an organic cation is meglumine (1-deoxy-1-methylamino-sorbitol).

A further iteration of this embodiment relates to cations formed from amino acids. Non-limiting examples include lysine, ornithine, arginine, glutamine, and the like.

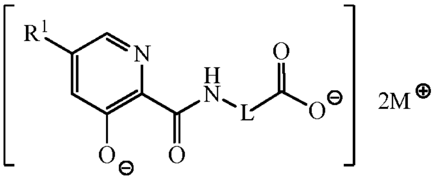
Another aspect of organic amines suitable for forming salts of the disclosed stabilizer include amines wherein one or more of R^a, R^b and R^c are taken together to form a heterocyclic ring that can comprise from 3 to 20 atoms and optionally one or more heteroatoms chosen from nitrogen, oxygen and sulfur. Non-limiting examples include piperazine, piperidine, morpholine, thiomorpholine, and the like.

In addition, di-valent cations can be used wherein the salts of these examples have the formula:

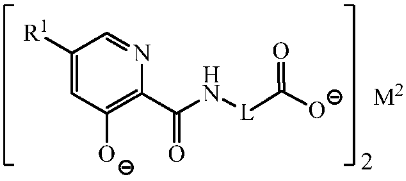


Non-limiting examples of di-valent cations includes calcium magnesium, barium and the like.

Another example of salts includes the di-anions having the formula:



and



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wherein M is the same as defined herein above.

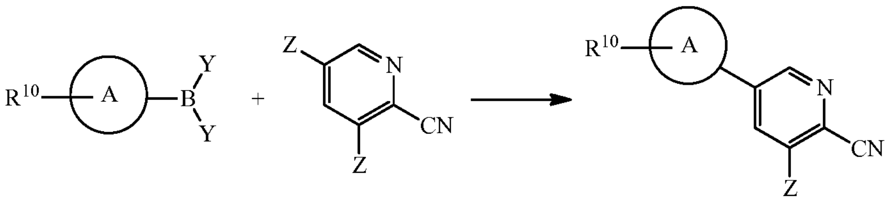
The importance of the herein disclosed intermediates lies in the fact that the formulator can prepare an admixture comprising a plurality of final compounds in one step by the choice of reactants in the final process step as described herein. For example, it is known by the artisan that, although two or more analogs can have approximately equal pharmacological activity, other properties such as bioavailability can be different. Using the disclosed intermediates to form admixtures of final analogs can provide the formulator with a final composition which utilizes the disparate pharmacological activities of the molecules to provide for a constant level of a desired property. For example, one analog in the admixture can have immediate bioavailability while a second or third compound has a slower bioavailability which can provide a pharmacologically active composition that has a steady or near steady level of drug active in a user.

PROCESS

Disclosed herein is a process for preparing the herein above disclosed [(5-phenyl-3-hydroxypyridine-2-carbonyl)-amino]alkanoic acids and [(5-heteroaryl-3-hydroxypyridine-2-carbonyl)-amino]alkanoic acids. As disclosed herein, the 5-phenyl and 5-heteroaryl rings can be substituted by one or more independently chosen substitutions for hydrogen.

The following is a summary of the steps that comprise the disclosed process.

Step A



A1 A2 A3

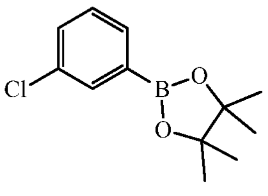
Step A relates to the condensation of an aryl or heteroaryl borate precursor, A1, and a 3,5-dihalo-2-cyanopyridine, A2, wherein each Z is independently chloro or bromo, to form a 5-aryl or 5-heteroaryl-3-halo-2-cyanopyridine, A3.

The borate precursor, A1, comprises ring A wherein ring A can be:

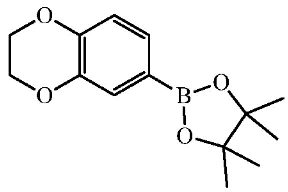
A) substituted or unsubstituted C_6 or C_{10} aryl; and

ii) substituted or unsubstituted C_1-C_9 heteroaryl;

wherein the substitutes for hydrogen atoms on the A ring are one or more R^{10} units that are independently chosen and further described herein. Y is OR^{20}, wherein R^{20} is hydrogen or C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, or two OR^{20} units can be taken together to form a 5-member to 7-member C_3-C_{10} cyclic ester, for example, a cyclic ester having the formula:



or



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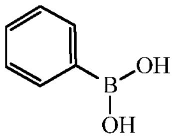
One aspect of borate precursors relates to phenyl boronic acid having the formula:



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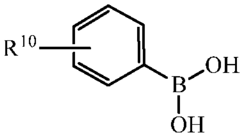
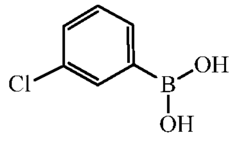
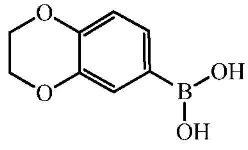
Another aspect of borate precursors relates to substituted boronic acids having the formula:



wherein R^{10} represents from 1 to 5 substitutions as defined herein above. Non-limiting examples of this aspect includes borate precursors having the formula:



and



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The 3,5-dihalo-2-cyanopyridine, A2, is chosen from 3,5-dichloro-2-cyanopyridine, 3-chloro-5-bromo-2-cyanopyridine, 3,5-dibromo-2-cyanopyridine and 3-bromo-5-chloro-2-cyanopyridine.

Step A is conducted in the presence of a catalyst, for example, a Suzuki coupling catalyst. The formulator can choose the catalyst and conditions that are compatible with the reagents, *i.e.*, borate precursor and 3,5-dihalo-2-cyanopyridine. (See, Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419-422; Suzuki, A., *J. Organometallic Chem.* **1999**, *576*, 147–168; Barder, T. E. *et al.*, "Catalysts for Suzuki-Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure," *J. Am. Chem. Soc.* **2005**, 127, 4685-4696 included herein by reference in their entirety.)

In one embodiment, the catalyst is [1,1'-bis(diphenyphosphino)ferrocene]dichloropalladium(II) [$PdCl_2$(dppf)].

Another category of catalysts include ortho-metalated catalysts with alkylphosphine ligands of the general formula $[Pd(X)(\kappa^2 N,C\text{-}C_6H_4CH_2NMe_2)(PR_3)]$ wherein R is Cy, X is trifluoroacetate, trifluoromethanesufonyl, chloro, or iodo; PR_3 is PCy_2(*o*-biphenyl), X is trifluoroacetate). Non-limiting examples of this category include $[\{Pd(\mu\text{-}TFA)(\kappa^2 N,C\text{-}C_6H_4CH_2NMe_2)\}_2]$ and $[\{Pd(TFA)(\kappa^2 N,C\text{-}C_6H_4CH{=}N^iPr)\}_2]$.

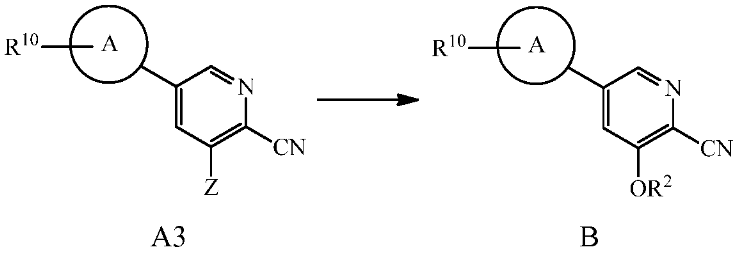
The catalyst can be preformed, for example, purchased from a chemical supplier or the catalyst can be generated *in situ*. One non-limiting example of Step A wherein the catalyst is generated *in situ* includes the following procedure. $Pd(OAc)_2$ (1.5 mmol %), 3,3'-dimethyl-1,1'(2,4-bismethylenemesitylene)(4,4,5,6-tetrahydropyrimidinium) chloride (1.5 mmol %), a borate precursor (1.5 mmol), a 3,5-dihalo-2-cyanopyridine (1.0 mmol), K_2CO_3 (2 mmol), water (3 mL)-DMF (3 mL) are added to a small Schlenk tube and the mixture heated at 80 °C for 5 hours. At the conclusion of the reaction, the mixture is collected, removed by extraction with suitable solvent, and the desired product isolated by methods known to the artisan.

Step A is conducted in the presence of a base. Non-limiting examples of suitable bases that can be used in Step A includes LiOH, NaOH, KOH, $Ca(OH)_2$, Li_2CO_3, Na_2CO_3, K_2CO_3, and $CaCO_3$. In one embodiment, the base is K_2CO_3. In another embodiment, the base is Na_2CO_3.

Step A can be optionally conducted in the presence of a solvent. Non-limiting examples of solvents include water, formic acid, acetic acid; alcohols, for example, methanol, ethanol, 2,2,2-trichlorethanol, propanol, isopropanol, butanol, *tert*-butanol, and the like; ketones, for example, acetone, methyl ethyl ketone, diethyl ketone, and the like; esters, for example, methyl acetate, ethyl acetate, methyl propionate, ethyl propionate, and the like; ethers, for example, diethyl ether, methyl *tert*-butyl ether, tetrahydrofuran, dimethoxyethane, bis(2-methoxyethyl) ether (diglyme), 1,4-dioxane,and the like; alkanes, for example, pentane, isopentane, petroleum ether, hexane, mixtures of hexanes, cyclohexane, 35eptanes, isoheptane, octane, isooctane, and the like; halogenated solvents, for example, dichloromethane, chloroform, carbon tetrachloride, 1,1-dichloroethane, 1,1,1-trichloroethane, 1,2-dichloroethane, chlorobenzene, and the like; aromatic hydrocarbons, for example, benzene, toluene, 1,2-dimethylbenzene (*ortho*-xylene), 1,3-dimethylbenzene (*meta*-xylene), 1,4-dimetylbenzene (*para*-xylene), nitrobenzene, and the like; dipolar aprotic solvents, for example, acetonitrile, dimethylsulfoxide, *N,N*-dimethylformamide, *N,N*-diethylformamide, *N,N*-dimethylacetamide, *N,N*-diethylacetamide, *N*-methyl-2-pyrrolidinone, carbon disulfide, and hexamethylphosphoramide; and mixtures of one or more solvents.

The reaction can be conducted at any temperature sufficient to provide the desired products or desired products.

Step B



Step B relates to the conversion of a 5-aryl or 5-heteroaryl-3-halo-2-cyanopyridine, A3, to a 5-aryl or 5-heteroaryl-3-alkoxy-2-cyanopyridine, B.

Compound A3 is reacted with an alkoxide having the formula:

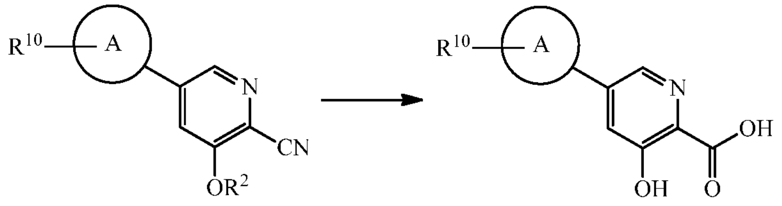
$$^{\ominus}OR^2$$

wherein R^2 is C_1-C_{12} linear alkyl or C_3-C_{12} branched alkyl. In one embodiment of step B, intermediate A3 can be reacted with methoxide anion. The methoxide anion can be generated *in situ*, for example, by the addition of an alkali metal to methanol. In one example, from 1 equivalent to 10 equivalents of sodium metal based upon the amount of A3 to be converted in Step B, is added to an excess of methanol. In another example, an alkali metal is added to an excess of methanol, the solvent removed, and the resulting sodium methoxide retained for use when, for example, Step B is conducted in a solvent other than methanol.

In another embodiment, the intermediate A3 can be reacted with ethoxide anion generated from ethanol. In still another embodiment, the intermediate A3 can be reacted with isopropoxy anion generated from isopropanol.

As such, step B can be conducted at any temperature sufficient to provide the desired products or desired products. In addition, step B can be conducted in any solvent or mixtures of solvents that do not react with methoxide anion under the conditions chosen by the formulator.

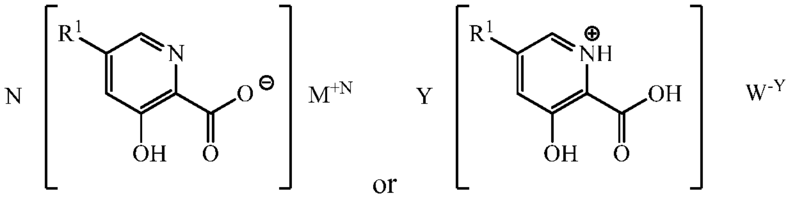
Step C



B C

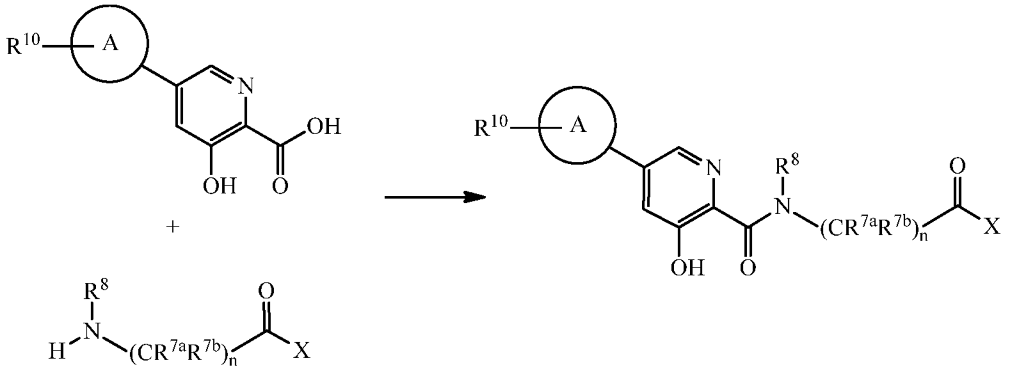
Step C relates to the conversion of the 5-aryl or 5-heteroaryl-3-alkoxy-2-cyanopyridine formed in step B to form a 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine, C, (5-aryl or 5-heteroaryl-3-hydroxypicolinic acid). This conversion can be conducted in the presence of any acid capable of hydrolysis of the cyano moiety to a carboxylic acid moiety and the methoxy moiety to a hydroxyl moiety. In one embodiment, 48% aqueous HBr can be used. In another embodiment, 37% aqueous HCl can be used.

The compounds having formula C can be isolated as the free acid or as a salt, for example, as a compound having the formula:



as further described herein. Depending upon the intended use of the products of step C, the formulator can proceed to step D or retain the products of step C for use in preparing admixtures of prolyl hydroxylase inhibitors or for preparing prodrugs of prolyl hydroxylase inhibitors.

Step D



D1 D2

Step D relates to the reaction of the 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine formed in step C with a compound having formula D1, wherein X is chosen from –OH, –OR^3, –NR^{4}R^5 or –OM^1 as defined herein above, to form one of the following:

i) a prolyl hydroxylase inhibitor;

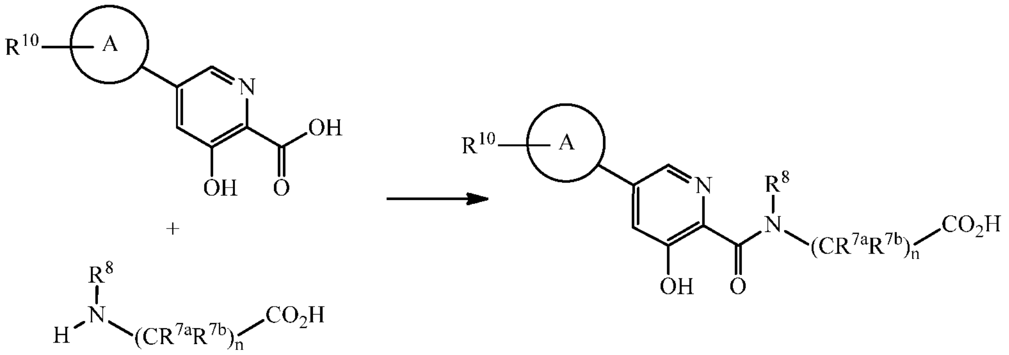
ii) a prolyl hydroxylase inhibitor prodrug;

iii) an admixture of prolyl hydroxylase inhibitors;

iv) an admixture of prolyl hydroxylase inhibitor prodrugs; or

v) suitable pharmaceutical salts thereof.

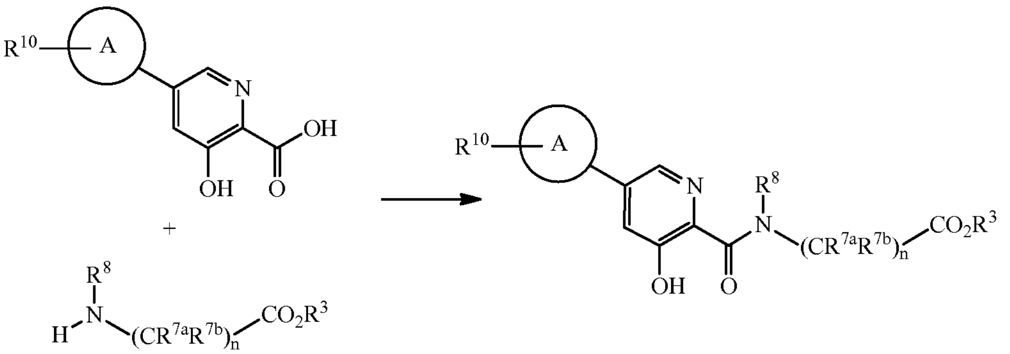
One aspect of step D relates to formation of a prolyl hydroxylase inhibitor according to the following scheme:



D

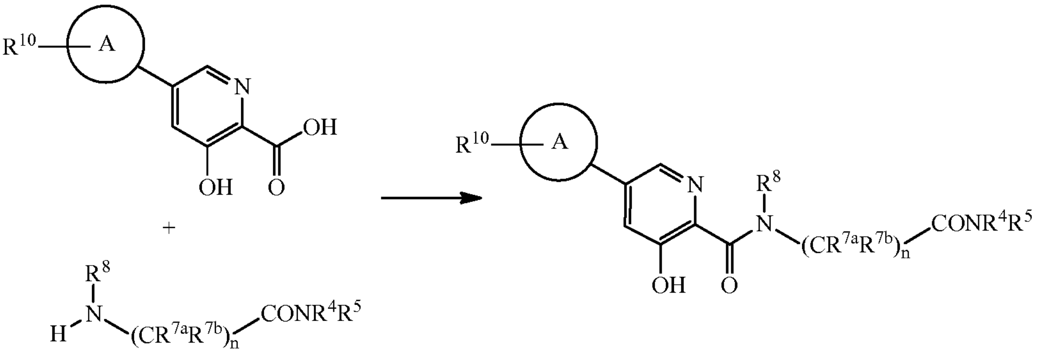
wherein R^{7a}, R^{7b}, R^8 and the index n are defined herein above.

Another aspect of step D relate to formation of a prolyl hydroxylase ester prodrug according to the following scheme:



wherein R^3, R^{7a}, R^{7b}, R^8 and the index n are defined herein above.

A further aspect of step D relate to formation of a prolyl hydroxylase amide prodrug according to the following scheme:



wherein R^4, R^5, R^{7a}, R^{7b}, R^8 and the index n are defined herein above.

Step D relates to the coupling of a 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxy-pyridine, C, prepared in Step C with an amino acid, amino acid ester, or amino acid amide. Any coupling reagent compatible with the 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxy-pyridine, amino acid, amino acid ester, or amino acid amide can be used to prepare the desired prolyl hydroxylase inhibitors or prodrugs thereof. Non-limiting examples of coupling reagents includes carbonyldiimidazole (CDI), dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), and ethyl-(N',N'-dimethylamino)propylcarbodiimide (EDC), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), O-(benzotriazol-1-yl)-N,N,N'N'-tertaetyluronium hexafluorophosphate (HBTU), O-(benzotriazol-1-yl)-N,N,N'N'-tertamethyluronium tetrafluoroborate (TBTU), O-(7-azabenzotriazol-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate (HATU), O-(6-chlorobenzotriazol-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate (HCTU), O-(3,4-dihydro-4-oxo-1,2,3-benzotriazine-3-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate (TDBTU), and 3-(diethylphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-

one (DEPBT). In one iteration, wherein R^8 is not hydrogen, step D can be conducted with a suitable reagent such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP).

A further iteration of the reaction outlined in step D utilizes an *in situ* generated mixed anhydride of the 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine, for example, reacting compound C with a mixed anhydride forming reagent. Non-limiting examples include isobutylchloro-formate (IBCF), ethylchoroformate, isopropylchloroformate, and the like. Other coupling reagents include 2-chloro-3,6-dimethoxy-1,3,5-triazine, pivalolyl chloride and triphosgene. In another iteration, acyl chlorides can be used to activate the carbonyl moiety of compound C for the coupling exemplified in step D.

In a yet further embodiment pivaloyl chloride in THF are used to catalyze the coupling reaction.

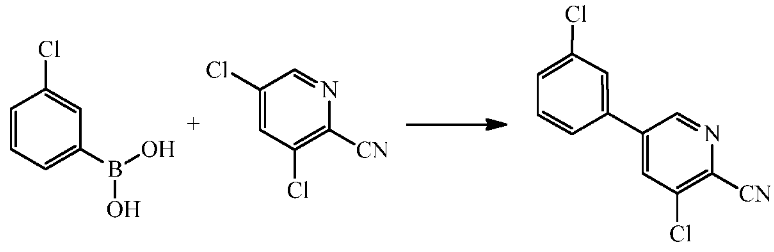
An organic or inorganic base can be used for conducting step D. Non-limiting examples of suitable organic bases include diisopropylethylamine, and the like.

Step D can be conducted in one or more solvents. Non-limiting examples of solvents include dimethylformamide (DMF), diethylformamide (DEF), dimethylacetamide (DMA), diethylacetamide(DEA), dimethyl sulfoxide(DMSO), dioxane, and water. In one embodiment, a mixture of water and one or more polar organic solvents can be used, for example, DMF/water, DMSO/water, dioxane/water, DMF/dioxane/water, and the like.

In some embodiments of the disclosed process, due to the type of substitution R^{10} on ring A, the formulator can form a prodrug prior then further process the prodrug to the final prolyl hydroxylase inhibitor. For example, the intermediate C may comprise an R^{10} unit that has a protecting group present, *i.e.*, carbobenzyloxy, *tert*-butoxycarbonyl, and the like. In such examples it can be more convenient for the formulator to form the final product in prodrug form, remove the protecting group then in a Step E, hydrolyze the prodrug to the free acid. The hydrolysis can be conducted in any suitable acid or base.

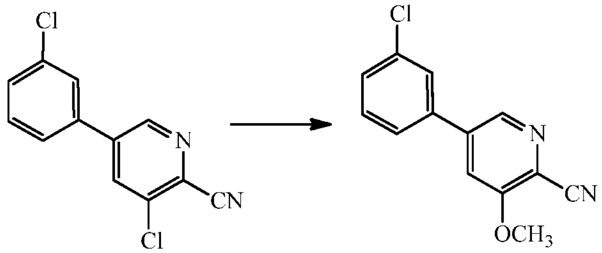
The conditions of Step D can be modified by the formulator to meet the properties of the reagents.

Scheme I herein below outlines and Example 1 describes a non-limiting example of the disclosed process for the preparation of a prolyl hydroxylase ester pro-drug.



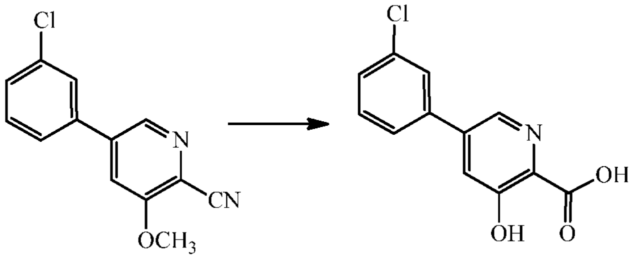
1

Reagents and conditions: (a) K_2CO_3, $PdCl_2$(dppf), DMF; 45 °C, 18 hr.



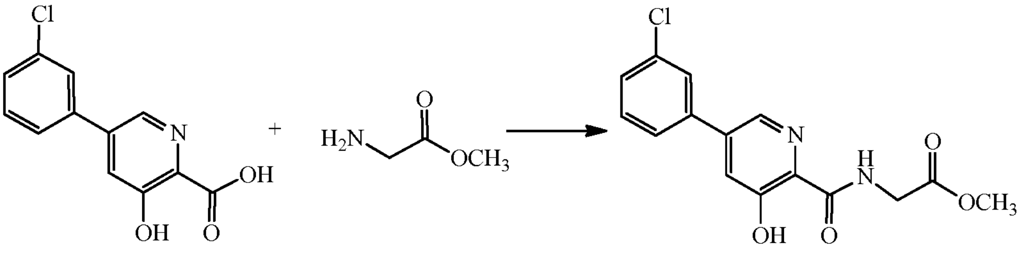
1 **2**

Reagents and conditions: (b) $NaOCH_3$, CH_3OH; reflux, 20 hr.



2 **3**

Reagents and conditions: (c) 48% HBr; reflux, 20 hr.



3 **4**

Reagents and conditions: (d) CDI, DIPEA, DMSO; rt, 2.5 hr.

EXAMPLE 1

Methyl {[5-(3-chlorophenyl)-3-hydroxypyridin-2-yl]amino}acetate (4)

Preparation of 5-(3-chlorophenyl)-3-chloro-2-cyanopyridine (1): To a 100 mL round bottom flask adapted for magnetic stirring and equipped with a nitrogen inlet was charged (3-chlorophenyl)boronic acid (5 g, 32 mmol), 3,5-dichloro-2-cyanopyridine (5.8 g, 34 mmol), K_2CO_3 (5.5 g, 40 mmol), [1,1'-bis(diphenyphosphino)ferrocene]dichloro-palladium(II) [$PdCl_2$(dppf)] (0.1 g, 0.13 mmol), dimethylformamide (50 mL) and water (5mL). The reaction solution was agitated and heated to 45 °C and held at that temperature for 18 hours after which the reaction was determined to be complete due to the disappearance of 3,5-dichloro-2-cyanopyridine as measured by TLC analysis using ethyl acetate/methanol (4:1) as the mobile phase and UV 435 nm to visualize the reaction components. The reaction solution was then cooled to room temperature and the contents partitioned between ethyl acetate (250 mL) and saturated aqueous NaCl (100 mL). The organic phase was isolated and washed a second time with saturated aqueous NaCl (100 mL). The organic phase was dried for 4 hours over $MgSO_4$, the $MgSO_4$ removed by filtration and the solvent removed under reduced pressure. The residue that remained was then slurried in methanol (50 mL) at room temperature for 20 hours. The resulting solid was collected by filtration and washed with cold methanol (50 mL) then hexanes (60 mL) and dried to afford 5.8 g (73% yield) of an admixture containing a 96:4 ratio of the desired regioisomer. ^{1}H NMR (DMSO-d_6) δ 9.12 (d, 1H), 8.70 (d, 1H), 8.03 (t, 1H) 7.88 (m, 1H), and 7.58 (m, 2H).

Preparation of 5-(3-chlorophenyl)-3-methoxy-2-cyanopyridine (2): To a 500 mL round bottom flask adapted for magnetic stirring and fitted with a reflux condenser and nitrogen inlet was charged with 5-(3-chlorophenyl)-3-chloro-2-cyanopyridine, **1**, (10 g, 40 mmol), sodium methoxide (13.8 mL, 60 mmol) and methanol (200 mL). With stirring, the reaction solution was heated to reflux for 20 hours. The reaction was determined to be complete due to the disappearance of 5-(3-chlorophenyl)-3-chloro-2-cyanopyridine as measured by TLC analysis using hexane/ethyl acetate (6:3) as the mobile phase and UV 435 nm to visualize the reaction components. The reaction mixture was cooled to room temperature and combined with water (500 mL). A solid began to form. The mixture was cooled to 0 °C to 5 °C and stirred for 3 hours. The resulting solid was collected by filtration and washed with water, then hexane. The resulting cake was dried *in vacuo* at 40 °C to afford 9.4 g (96% yield) of the desired product as an off-white solid. ^{1}H NMR (DMSO-d_6)

δ 8.68 (d, 1H), 8.05 (d, 1H), 8.01 (s, 1H) 7.86 (m, 1H), 7.59 (s, 1H), 7.57 (s, 1H) and 4.09 (s, 3H).

Preparation of 5-(3-chlorophenyl)-3-hydroxypyridine-2-carboxylic acid (3): To a 50 mL round bottom flask adapted for magnetic stirring and fitted with a reflux condenser was charged 5-(3-chlorophenyl)-3-methoxy-2-cyanopyridine, **2**, (1 g, 4 mmol) and a 48% aqueous solution of HBr (10 mL). While being stirred, the reaction solution was heated to reflux for 20 hours. The reaction was determined to be complete due to the disappearance of 5-(3-chlorophenyl)-3-methoxy-2-cyanopyridine as measured by TLC analysis using hexane/ethyl acetate (6:3) as the mobile phase and UV 435 nm to visualize the reaction components. The reaction contents was then cooled to 0 °C to 5 °C with stirring and the pH was adjusted to approximately 2 by the slow addition of 50% aqueous NaOH. Stirring was then continued at 0 °C to 5 °C for 3 hours. The resulting solid was collected by filtration and washed with water, then hexane. The resulting cake was dried *in vacuo* at 40 °C to afford 1.03 g (quantitative yield) of the desired product as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.52 (d, 1H), 7.99 (d, 1H), 7.95 (s, 1H) 7.81 (t, 1H), 7.57 (s, 1H), and 7.55 (s, 1H).

Preparation of methyl {[5-(3-chlorophenyl)-3-hydroxypyridin-2-yl]amino}acetate (4): To a 50 mL round bottom flask adapted for magnetic stirring and fitted with a nitrogen inlet tube was charged 5-(3-chlorophenyl)-3-hydroxypyridine-2-carboxylic acid, 3, (1 gm, 4 mmol), *N,N'*-carbonyldiimidazole (CDI) (0.97 g, 6 mmol) and dimethyl sulfoxide (5 mL). The reaction mixture was stirred at 45 °C for about 1 hour then cooled to room temperature. Glycine methyl ester hydrochloride (1.15 g, 12 mmol) is added followed by the dropwise addition of diisopropylethylamine (3.2 mL, 19 mmol). The mixture was then stirred for 2.5 hours at room temperature after which water (70 mL) was added. The contents of the reaction flask was cooled to 0 °C to 5 °C and 1N HCl was added until the solution pH is approximately 2. The solution was extracted with dichloromethane (100 mL) and the organic layer was dried over $MgSO_4$ for 16 hours. Silica gel (3 g) is added and the solution slurried for 2 hours after which the solids are removed by filtration. The filtrate is concentrated to dryness under reduced pressure and the resulting residue was slurried in methanol (10 mL) for two hours. The resulting solid was collected by filtration and washed with cold methanol (20 mL) then hexane and the resulting cake is dried to afford 0.85 g of the desired product as an off-white solid. The filtrate was treated to afford 0.026 g of the desired product as a second crop. The combined crops afford 0.88 g (68% yield) of the desired product. ^{1}H NMR (DMSO-d_6) δ 12.3 (s, 1H), 9.52 (t, 1H), 8.56 (d, 1H), 7.93 (s, 1H), 7.80 (q, 2H), 7.55 (t, 2H), 4.12 (d, 2H), and 3.69 (s, 3H).

The formulator can readily scale up the above disclosed synthesis. Disclosed herein below is a synthesis wherein the disclosed process is scaled up for commercial use.

EXAMPLE 2

Methyl {[5-(3-chlorophenyl)-3-hydroxypyridin-2-yl]amino}acetate (4)

Preparation of 5-(3-chlorophenyl)-3-chloro-2-cyanopyridine (1): A 20 L reactor equipped with a mechanical stirrer, dip tube, thermometer and nitrogen inlet was charged with (3-chlorophenyl)boronic acid (550 g, 3.52 mol), 3,5-dichloro-2-cyanopyridine (639 g, 3.69 mol), K_2CO_3 (5.5 g, 40 mmol), [1,1'-bis(diphenyphosphino)ferrocene]dichloro-palladium(II) [$PdCl_2$(dppf)] (11.5 g, 140 mmol), and dimethylformamide (3894 g, 4.125 L). The reaction solution was agitated and purged with nitrogen through the dip-tube for 30 minutes. Degassed water (413 g) was then charged to the reaction mixture while maintaining a temperature of less than 50 °C 25 hours. The reaction was determined to be complete due to the disappearance of 3,5-dichloro-2-cyanopyridine as measured by TLC analysis using ethyl acetate/methanol (4:1) as the mobile phase and UV 435 nm to visualize the reaction components. The reaction solution was then cooled to 5 °C and charged with heptane (940 g, 1.375 L) and agitated for 30 minutes. Water (5.5 L) was charged and the mixture was further agitated for 1 hour as the temperature was allowed to rise to 15 °C. The solid product was isolated by filtration and washed with water (5.5 L) followed by heptane (18881 g, 2750 ML). The resulting cake was air dried under vacuum for 18 hours and then triturated with a mixture of 2-propanol (6908 g, 8800 mL0 and heptane (1 g, 2200mL0 at 50 °C for 4 hours, cooled to ambient temperature and then agitated at ambient temperature for 1 hour. The product was then isolated by filtration and washed with cold 2-propanol (3450 g, 4395 mL) followed by heptane (3010 g, 4400mL). The resulting solid was dried under high vacuum at 40 °C for 64 hours to afford 565.9 g (65% yield) of the desired product as a beige solid. Purity by HPLC was 98.3. ^{1}H NMR (DMSO-d_6) δ 9.12 (d, 1H), 8.70 (d, 1H), 8.03 (t, 1H) 7.88 (m, 1H), and 7.58 (m, 2H).

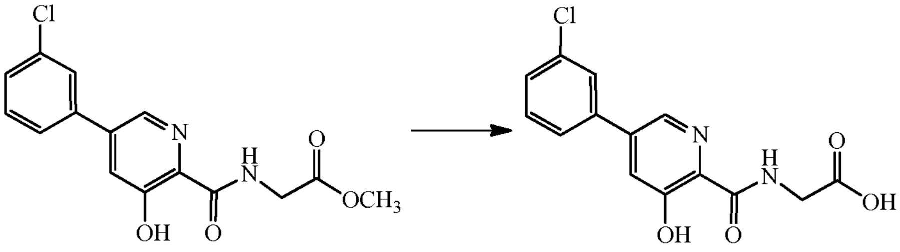
Preparation of 5-(3-chlorophenyl)-3-methoxy-2-cyanopyridine (2): A 20 L reactor equipped with a mechanical stirred, condenser, thermometer and nitrogen inlet was charged with 5-(3-chlorophenyl)-3-chloro-2-cyanopyridine, 1, (558 g, 2.24 mol) and sodium methoxide (25% solution in methanol, 726.0 g, 3.36 mol). With agitation, the reaction solution was heated to reflux for 24 hours, resulting in a beige-colored suspension. The reaction was determined to be complete due to the disappearance of 5-(3-chlorophenyl)-3-chloro-2-cyanopyridine as measured by TLC analysis using hexane/ethyl acetate (6:3) as the mobile phase and UV 435 nm to visualize the reaction components. The reaction mixture was cooled to 5 °C and then charged with water (5580 mL). The resulting slurry was agitated for 3 hours at 5 °C. The solid product was isolated by filtration and washed with water (5580 mL) until the filtrate had a pH of 7. The filter cake was air dried under vacuum for 16 hours. The filter cake was then charged back to the reactor and triturated in MeOH (2210 g, 2794 mL) for 1 hour at ambient temperature. The solid was collected by filtration and washed with MeOH (882 g, 1116 mL, 5 °C) followed by heptane (205 mL, 300mL), and dried under high vacuum at 45 °C for 72 hours to afford 448 g (82% yield) of the desired product as an off-white solid. Purity by HPLC was 97.9%. ^{1}H NMR (DMSO-d_6) δ 8.68 (d, 1H), 8.05 (d, 1H), 8.01 (s, 1H) 7.86 (m, 1H), 7.59 (s, 1H), 7.57 (s, 1H) and 4.09 (s, 3H).

Preparation of 5-(3-chlorophenyl)-3-hydroxypyridine-2-carboxylic acid (3): A 20 L reactor equipped with a mechanical stirrer, condenser, thermometer, nitrogen inlet and 25% aqueous NaOH trap was charged 5-(3-chlorophenyl)-3-methoxy-2-cyanopyridine, 2, (440.6 g, 1.8 mol) and 37% aqueous solution of HCl (5302 g). While being agitated, the reaction solution was heated to 102 °C for 24 hours. Additional 37% aqueous HCl (2653 g) was added followed by agitation for 18 hours at 104 °C. The reaction contents was then cooled to 5 °C, charged with water (4410 g) and then agitated at 0 °C for 16 hours. The resulting precipitated product was isolated by filtration and washed with water until the filtrate had a pH of 6 (about 8,000 L of water). The filter cake was pulled dry under reduced pressure for 2 hours. The cake was then transferred back into the reactor and triturated in THF (1958 g, 2201 mL) at ambient temperature for 2 hours. The solid product was then isolated by filtration and washed with THF (778 g, 875 mL) and dried under reduced pressure at 5 °C for 48 hours to afford 385 g (89% yield) of the desired product as an off-white solid. HPLC purity was 96.2%. ^{1}H NMR (DMSO-d_6) δ 8.52 (d, 1H), 7.99 (d, 1H), 7.95 (s, 1H) 7.81 (t, 1H), 7.57 (s, 1H), and 7.55 (s, 1H).

Preparation of methyl {[5-(3-chlorophenyl)-3-hydroxypyridin-2-yl]amino}acetate (4): A 20 L reactor equipped with a mechanical stirrer, condenser, thermometer and nitrogen inlet was charged with 5-(3-chlorophenyl)-3-hydroxypyridine-2-carboxylic acid, 3, (380 g, 1.52 mol) and diisopropylethylamine (DIPEA)(295 g, 2.28 mol). With agitation, the solution was cooled to 3 °C and charged with trimethylacetyl chloride (275.7 g, 2.29 mol) while maintaining a temperature of less than 11 °C, The mixture was then agitated at ambient temperature for 2 hours. The mixture was then cooled to 10 °C and charged with a slurry of glycine methyl ester HCl (573.3 g, 4. 57 mol) and THF (1689 g, 1900mL), then charged with DIPEA (590.2 g, 4.57 mol) and agitated at ambient temperature for 16 hours. The mixture was then charged with EtOH (1500 g, 1900 mL) and concentrated under reduced pressure to a reaction volume of about 5.8 L. The EtOH addition and concentration was repeated twice more. Water (3800g) was then added and the mixture was agitated for 16 hours at ambient temperature. The resulting solid product was isolated by filtration and washed with a mixture of EtOH (300g, 380 mL) and water (380 g), followed by water (3800g), dried under reduced pressure for 18 hours at 50 °C to afforded 443 g (91% yield) of the desired product as an off-white solid. Purity by HPLC was 98.9%. ^{1}H NMR (DMSO-d_6) δ 12.3 (s, 1H), 9.52 (t, 1H), 8.56 (d, 1H), 7.93 (s, 1H), 7.80 (q, 2H), 7.55 (t, 2H), 4.12 (d, 2H), and 3.69 (s, 3H).

Scheme II herein below outlines and Example 2 describes a non-limiting example of the disclosed process for preparing a prolyl hydroxylase inhibitor from an ester prodrug.

Scheme II



4 5

Reagents and conditions: (a) NaOH, THF; 2 hr.

EXAMPLE 3

{[5-(3-Chlorophenyl)-3-hydroxypyridin-2-yl]amino}acetic acid (5)

Preparation of {[5-(3-chlorophenyl)-3-hydroxypyridin-2-yl]amino}acetic acid (5): To a 50 mL flask is charged methyl {[5-(3-chlorophenyl)-3-hydroxypyridin-2-yl]amino}-acetate, 4, (0.45 g, 1.4 mmol), tetrahydrofuran (4.5 mL) and 1 M NaOH (4.5 mL, 4.5 mmol). The mixture was stirred for 2 hours at room temperature after which it was determined by TLC analysis using hexane/ethyl acetate (6:3) as the mobile phase and UV 435 nm to visualize the reaction components that the reaction was complete. The reaction solution was adjusted to pH 1 with concentrated HCl and the solution was heated at 35 °C under vacuum until all of the tetrahydrofuran had been removed. A slurry forms as the solution is concentrated. With efficient stirring the pH is adjusted to ~2 with the slow addition of 1 M NaOH. The solid which forms was collected by filtration, washed with water, followed by hexane, then dried under vacuum to afford 0.38 g (88% yield) of the desired product as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.84 (s, 1H), 12.39 (s, 1H), 9.39 (t, 1H), 8.56 (d, 1H), 7.94 (s, 1H), 7.81 (m, 2H), 7.55 (q, 2H), and 4.02 (d, 2H).

The formulator can readily scale up the above disclosed synthesis. Disclosed herein below is a synthesis wherein the disclosed process is scaled up for commercial use.

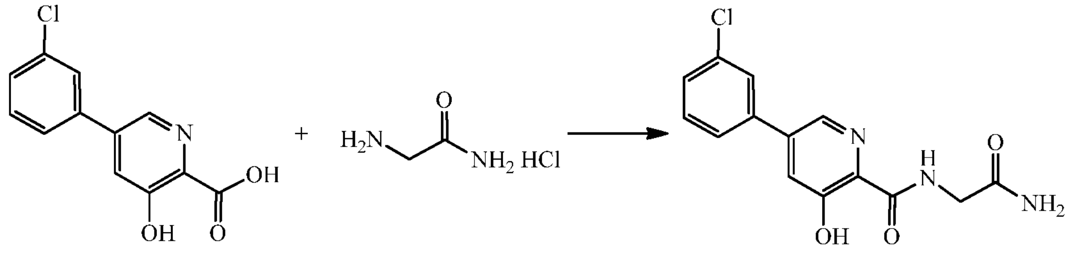
EXAMPLE 4

{[5-(3-Chlorophenyl)-3-hydroxypyridin-2-yl]amino}acetic acid (5)

Preparation of {[5-(3-chlorophenyl)-3-hydroxypyridin-2-yl]amino}acetic acid (5): To a 20 L reactor equipped with a mechanical stirrer, condenser, thermometer and nitrogen inlet was charged methyl {[5-(3-chlorophenyl)-3-hydroxypyridin-2-yl]amino}-acetate, 4, (440 g, 1.42 mol), tetrahydrofuran (3912 g, 4400 mL) and 1 M NaOH (4400 mL). The mixture was stirred for 2 hours at room temperature after which it was determined by TLC analysis using hexane/ethyl acetate (6:3) as the mobile phase and UV 435 nm to visualize the reaction components that the reaction was complete. The reaction solution was acidified to a pH of 2 with slow addition of 2M HCl (2359 g). The resulting mixture was concentrated under reduced pressure to a volume of about 7.5 L. Ware (2210 g) was added and the solution cooled to ambient temperature and agitated for 18 hours. The solid product was isolated by filtration and washed with water (6 L). the crude product was transferred back into the reactor and triturated with 2215 g o deionized water at 70 °C for 16 hours. The mixture was cooled to ambient temperature, The solid product was isolated by filtration and washed with water (500 mL) and dried under reduced pressure at 70 °C for 20 hours to afford 368 g (87% yield) of the desired product as an off-white solid. Purity by HPLC was 99.3%. ^{1}H NMR (DMSO-d_6) δ 12.84 (s, 1H), 12.39 (s, 1H), 9.39 (t, 1H), 8.56 (d, 1H), 7.94 (s, 1H), 7.81 (m, 2H), 7.55 (q, 2H), and 4.02 (d, 2H).

Scheme III herein below outlines and Example 3 describes a non-limiting example of the disclosed process for preparing a prolyl hydroxylase amide prodrug.

Scheme III



Reagents and conditions: (a) EDCI, HOBt, DIPEA, DMF; rt.

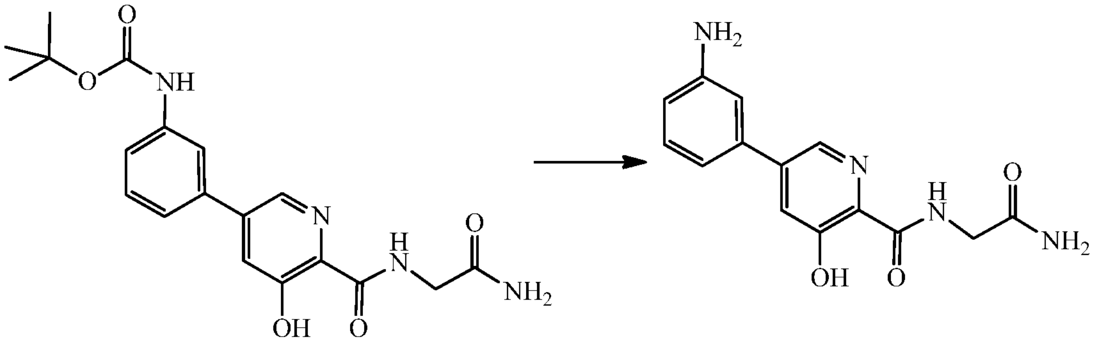
EXAMPLE 5

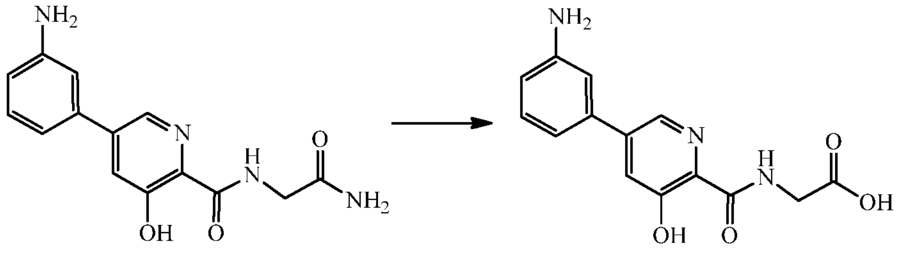
5-(3-Chlorophenyl)-*N*-(2-amino-2-oxoethyl)-3-hydroxylpyridin-2-yl amide

Preparation of 5-(3-chlorophenyl)-*N*-(2-amino-2-oxoethyl)-3-hydroxylpyridin-2-yl amide (6): To a solution of 5-(3-chlorophenyl)-3-hydroxypyridine-2-carboxylic acid, 3, (749 mg, 3 mmol) in DMF (20 mL) at room temperature under N_2 is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (0.925 g, 5.97 mmol) and 1-hydroxybenzotriazole (HOBt) (0.806 g, 5.97 mmol). The resulting solution is stirred for 15 minutes then 2-aminoacetamide hydrochloride (0.66 g, 5.97 mmol) and diisopropylethylamine (1.56 ml, 8.96 mmol) are added. The reaction is monitored by TLC and when the reaction is complete the reaction mixture is concentrated under reduced pressure and H_2O added. The product can be isolated by normal work-up: The following data have been reported for compound (6). ^{1}H NMR (250 MHz, DMSO-d_6) δ ppm 12.46 (1 H, s), 9.17 (1 H, t, $J = 5.9$ Hz), 8.55 (1 H, d, $J = 2.0$ Hz), 7.93 (1 H, d, $J = 0.9$ Hz), 7.75 – 7.84 (2 H, m), 7.49 – 7.60 (3 H, m), 7.18 (1 H, s), 3.91 (2 H, d, $J = 5.9$ Hz). HPLC-MS: *m/z* 306 $[M+H]^+$.

Scheme IV herein below depicts a non-limiting example the hydrolysis of an amide pro-drug to a prolyl hydroxylase inhibitor after removal of a R^{10} protecting group.

Scheme IV





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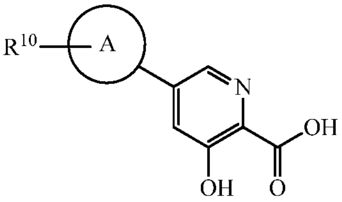
While particular embodiments of the present disclosure have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the disclosure. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this disclosure.

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein A is a ring chosen from:

i) C_6 or C_{10} aryl; or

ii) C_1-C_9 heteroaryl;

R^{10} units represent at least one optionally present substitutions for a ring hydrogen atom; or two R^{10} units can be taken together to form a substituted or unsubstituted C_4-C_8 cycloalkyl ring, a substituted or unsubstituted C_6 or C_{10} aryl ring, a substituted or unsubstituted C_2-C_8 heterocyclic ring, or a substituted or unsubstituted C_3 to C_5 heteroaryl ring, wherein the heterocyclic and heteroaryl rings comprise one or more hetero atoms independently chosen from oxygen (O), nitrogen (N), or sulfur (S).

2. The compound according to Claim 1, wherein A is a C_6 aryl ring.

3. The compound according to either Claim 1 or 2, wherein A is substituted by one or more R^{10} units independently chosen from:

i) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl;

ii) C_6 or C_{10} aryl;

iii) C_7 or C_{11} alkylenearyl;

iv) C_1-C_9 heterocyclic rings;

v) C_1-C_9 heteroaryl rings;

vi) $-(CR^{102a}R^{102b})_aOR^{101}$;

vii) $-(CR^{102a}R^{102b})_aC(O)R^{101}$;

viii) $-(CR^{102a}R^{102b})_aC(O)OR^{101}$;

ix) $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$;

x) $-(CR^{102a}R^{102b})_aN(R^{101})C(O)R^{101}$;

xi) $-(CR^{102a}R^{102b})_aN(R^{101})C(O)_2R^{101}$;

xii) $-(CR^{102a}R^{102b})_aN(R^{101})_2$;

xiii) halogen;

xiv) $-(CR^{102a}R^{102b})_I$;

xv) $-(CR^{102a}R^{102b})_aNO_2$;

xvi) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, j + k = 3; the index j' is an integer from 0 to 2, j' + k' = 2;

xvii) $-(CR^{102a}R^{102b})_aSR^{101}$;

xviii) $-(CR^{102a}R^{102b})_aSO_2R^{101}$; and

xix) $-(CR^{102a}R^{102b})_aSO_3R^{101}$;

wherein each R^{101} is independently hydrogen, substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, phenyl, benzyl, heterocyclic, or heteroaryl; or two R^{101} units can be taken together to form a ring comprising 3-7 atoms; R^{102a} and R^{102b} are each independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl; the index "a" is from 0 to 4.

4. The compound according to any of Claims 1 to 3, wherein A is substituted by one or more R^{10} units independently chosen from:

i) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl;

ii) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkoxy; or

iii) halogen.

5. The compound according to any of Claims 1 to 4, wherein ring A is chosen from 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 3,5-dichlorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,3,6-trichlorophenyl, 2,4,5-trichlorophenyl, 3,4,5-trichlorophenyl, and 2,4,6-trichlorophenyl.

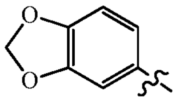
6. The compound according to any of Claims 1 to 4, wherein ring A is chosen from 2-chloro-3-methylphenyl, 2-chloro-4-methylphenyl, 2-chloro-5-methylphenyl, 2-chloro-6-methylphenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 3-chloro-5-methylphenyl, 3-chloro-6-methyl-phenyl, 2-fluoro-3-methylphenyl, 2-

fluoro-4-methylphenyl, 2-fluoro-5-methylphenyl, 2-fluoro-6-methylphenyl, 3-fluoro-2-methylphenyl, 3-fluoro-4-methylphenyl, 3-fluoro-5-methylphenyl, and 3-fluoro-6-methylphenyl.

7. The compound according to any of Claims 1 to 5, wherein ring A is chosen from 3-chlorophenyl, 3-fluorophenyl, 3-trifluoromethylphenyl, and 3-chloro-6-methylphenyl.

8. The compound according to Claim 1, wherein two R^{10} units are be taken together to form a substituted or unsubstituted C_2-C_8 heterocyclic ring, wherein the heterocyclic ring comprises one or more hetero atoms independently chosen from oxygen (O), nitrogen (N), or sulfur (S).

9. The compound according to either Claim 1 or 9, wherein two R^{10} units are taken together to form an A ring that has a formula chosen from: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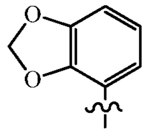
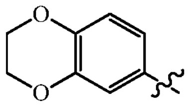
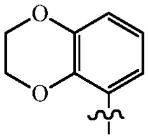

,

or

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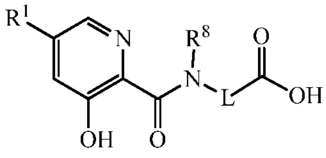
10. A process for preparing a compound having the formula:



wherein R^1 is chosen from:

i) substituted or unsubstituted C_6 or C_{10} aryl; or

ii) substituted or unsubstituted C_1-C_9 heteroaryl;

L is a linking unit having the formula:

$$-(CR^{7a}R^{7b})_n-$$

R^{7a} and R^{7b} are each independently:

i) hydrogen; or

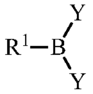
ii) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl;

R^8 is chosen from hydrogen, methyl, or ethyl; and

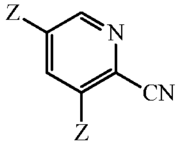
the index n is an integer from 1 to 4;

or a pharmaceutically acceptable salt thereof, comprising:

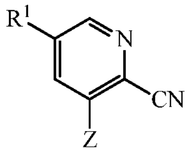
A) reacting a boronic acid or ester having the formula:



wherein Y is OR^{20}, R^{20} is hydrogen or C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, or two OR^{20} units can be taken together to form a 5-member to 7-member C_3-C_{10} cyclic ester, with a 3,5-dihalo-2-cyanopyridine having the formula:



each Z is independently chloro or bromo, in the presence of a catalyst, to form a 5-aryl or 5-heteroaryl-3-halo-2-cyanopyridine having the formula:

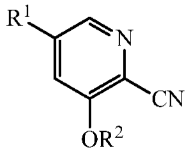


;

B) reacting the 5-aryl or 5-heteroaryl-3-halo-2-cyanopyridine formed in step (A) with an alkoxide anion having the formula:

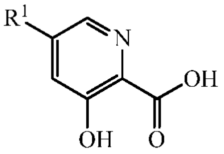
$$^{\ominus}OR^2$$

wherein R^2 is C_1-C_{12} linear alkyl or C_3-C_{12} branched alkyl, to form a 5-aryl or 5-heteroaryl-3-alkoxy-2-cyanopyridine having the formula:



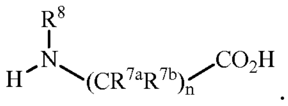
;

C) reacting the 5-aryl or 5-heteroaryl-3-alkoxy-2-cyanopyridine formed in step (B) with an acid to form a 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine having the formula:



; and

D) reacting the 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine formed in step (C) with an amino acid having the formula:



11. The process according to Claim 10, wherein the boronic acid in step (A) is a substituted or unsubstituted phenyl boronic acid.

12. The process according to either Claim 10 or 11, wherein the boronic acid in step (A) is a phenyl boronic acid substituted with one or more units independently chosen from:

i) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl;
ii) C_6 or C_{10} aryl;
iii) C_7 or C_{11} alkylenearyl;
iv) C_1-C_9 heterocyclic rings;
v) C_1-C_9 heteroaryl rings;
vi) $-(CR^{102a}R^{102b})_aOR^{101}$;
vii) $-(CR^{102a}R^{102b})_aC(O)R^{101}$;
viii) $-(CR^{102a}R^{102b})_aC(O)OR^{101}$;
ix) $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$;
x) $-(CR^{102a}R^{102b})_aN(R^{101})\,C(O)R^{101}$;
xi) $-(CR^{102a}R^{102b})_aN(R^{101})\,C(O)_2R^{101}$;
xii) $-(CR^{102a}R^{102b})_aN(R^{101})_2$;
xiii) halogen;
xiv) $-(CR^{102a}R^{102b})_I$;
xv) $-(CR^{102a}R^{102b})_aNO_2$;
xvi) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, j + k = 3; the index j' is an integer from 0 to 2, j' + k' = 2;
xvii) $-(CR^{102a}R^{102b})_aSR^{101}$;
xviii) $-(CR^{102a}R^{102b})_aSO_2R^{101}$; and
xix) $-(CR^{102a}R^{102b})_aSO_3R^{101}$;

wherein each R^{101} is independently hydrogen, substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, phenyl, benzyl, heterocyclic, or heteroaryl; or two R^{101} units can be taken together to form a ring comprising 3-7 atoms; R^{102a} and R^{102b} are each independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl; the index "a" is from 0 to 4

13. The process according to any of Claims 10 to 12, wherein the boronic acid in step (A) is substituted by one or more units independently chosen from:
    i) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl;
    ii) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkoxy; or
    iii) halogen.

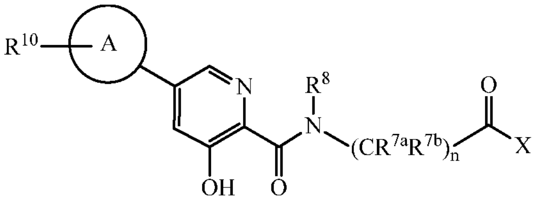
14. The process according to any of Claims 10 to 13, wherein the boronic acid in step (A) is chosen from 2-fluorophenylboronic acid, 3-fluorophenylboronic acid, 4-fluorophenylboronic acid, 2-chlorophenylboronic acid, 3-chlorophenylboronic acid, 4-chlorophenylboronic acid, 2-methylphenylboronic acid, 3-methylphenylboronic acid, 4-methylphenylboronic acid, 2-methoxyphenylboronic acid, 3-methoxyphenylboronic acid, 4-methoxyphenylboronic acid, 2-cyanophenylboronic acid, 3-cyanophenylboronic acid, 4-cyanophenylboronic acid, 2-nitrophenylboronic acid, 3-nitrophenylboronic acid, 4-nitrophenylboronic acid, 2-trifluoromethylphenylboronic acid, 3-trifluoromethylphenylboronic acid, 4-trifluoromethylphenylboronic acid, 2-carbamoylphenylboronic acid, 3-carbamoylphenylboronic acid, 4-carbamoylphenylboronic acid, 2-(pyrrolidine-1-carbonyl)phenylboronic acid, 3-(pyrrolidine-1-carbonyl)phenylboronic acid, 4-(pyrrolidine-1-carbonyl)phenylboronic acid, 2-(cyclopropanecarbonylamino)phenylboronic acid, 3-(cyclopropanecarbonylamino)phenylboronic acid, and 4-(cyclopropanecarbonylamino)phenylboronic acid.

15. The process according to any of Claims 10 to 14, wherein the catalyst in step (A) is [1,1'-bis(diphenyphosphino)ferrocene]dichloro-palladium(II).

16. The process according to any of Claims 10 to 15, wherein the alkoxide in step (B) is methoxide.

17. The process according to any of Claims 10 to 16, wherein the amino acid of step (D) is chosen from glycine, alanine, isoleucine, leucine, valine, 2-amino-2-methylpropanoic acid, 3-aminobutanoic acid, 3-amino-3-methylbutanoic acid, 3-amino-2-methylbutanoic acid, and 4-aminobutanoic acid.

18. A process for preparing a compound having the formula:



wherein A is a ring chosen from:

i) substituted or unsubstituted C_6 or C_{10} aryl; or

ii) substituted or unsubstituted C_1-C_9 heteroaryl;

R^{10} represents one or more independently chosen optionally present substitutions for hydrogen;

X is chosen from:

i) –OH;

ii) –OR^3;

iii) –NR^4R^5; and

iv) –OM^1;

R^3 is C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl; C_2-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkenyl; or C_2-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkynyl, or benzyl;

R^4 and R^5 are each independently hydrogen, C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl; C_2-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkenyl; or C_2-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkynyl; benzyl; or R^4 and R^5 can be taken together with the nitrogen atom to form a 3 to 10 member ring, wherein the ring can optionally contain one or more heteroatoms chosen from oxygen (O), nitrogen (N), or sulfur (S);

M^1 is a pharmaceutically acceptable cation;

R^{7a} and R^{7b} are each independently:

i) hydrogen; or

ii) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl;

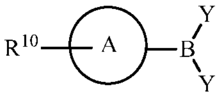
R^8 is chosen from hydrogen, methyl, or ethyl; and

the index n is an integer from 1 to 4;

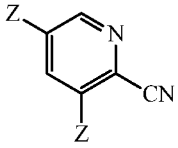
or a pharmaceutically acceptable salt thereof,

comprising:

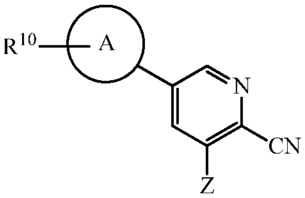
A) reacting a boronic acid or ester having the formula:



wherein Y is OR^{20}, R^{20} is hydrogen or C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, or two OR^{20} units can be taken together to form a 5-member to 7-member C_3-C_{10} cyclic ester, with a 3,5-dihalo-2-cyanopyridine having the formula:



each Z is independently chloro or bromo, in the presence of a catalyst, to form a 5-aryl or 5-heteroaryl-3-halo-2-cyanopyridine having the formula:

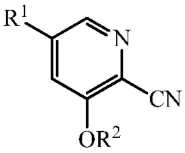


;

B) reacting the 5-aryl or 5-heteroaryl-3-halo-2-cyanopyridine formed in step (A) with an alkoxide anion having the formula:

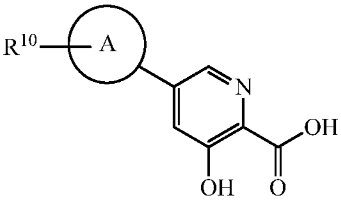
$$^{\ominus}OR^2$$

wherein R^2 is C_1-C_{12} linear alkyl or C_3-C_{12} branched alkyl, to form a 5-aryl or 5-heteroaryl-3-alkoxy-2-cyanopyridine having the formula:



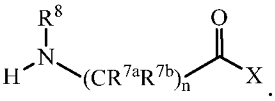
;

C) reacting the 5-aryl or 5-heteroaryl-3-alkoxy-2-cyanopyridine formed in step (B) with an acid to form a 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine having the formula:



; and

D) reacting the 5-aryl or 5-heteroaryl-3-hydroxy-2-carboxypyridine formed in step (C) with a compound having the formula:



.

19. The process according to Claim 18, wherein the boronic acid in step (A) is a substituted or unsubstituted phenyl boronic acid.

20. The process according to either Claim 18 or 19, wherein the boronic acid in step (A) is a phenyl boronic acid wherein R^{10} represents one or more substitutions for hydrogen independently chosen from:

i) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl;
ii) C_6 or C_{10} aryl;
iii) C_7 or C_{11} alkylenearyl;
iv) C_1-C_9 heterocyclic rings;
v) C_1-C_9 heteroaryl rings;
vi) $-(CR^{102a}R^{102b})_aOR^{101}$;
vii) $-(CR^{102a}R^{102b})_aC(O)R^{101}$;
viii) $-(CR^{102a}R^{102b})_aC(O)OR^{101}$;
ix) $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$;
x) $-(CR^{102a}R^{102b})_aN(R^{101})\,C(O)R^{101}$;
xi) $-(CR^{102a}R^{102b})_aN(R^{101})\,C(O)_2R^{101}$;
xii) $-(CR^{102a}R^{102b})_aN(R^{101})_2$;
xiii) halogen;
xiv) $-(CR^{102a}R^{102b})_I$;
xv) $-(CR^{102a}R^{102b})_aNO_2$;
xvi) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, j + k = 3; the index j' is an integer from 0 to 2, j' + k' = 2;
xvii) $-(CR^{102a}R^{102b})_aSR^{101}$;
xviii) $-(CR^{102a}R^{102b})_aSO_2R^{101}$; and
xix) $-(CR^{102a}R^{102b})_aSO_3R^{101}$;

wherein each R^{101} is independently hydrogen, substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, phenyl, benzyl, heterocyclic, or heteroaryl; or two R^{101} units can be taken together to form a ring comprising 3-7 atoms; R^{102a} and R^{102b} are each independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl; the index "a" is from 0 to 4

21. The process according to any of Claims 18 to 20, wherein R^{10} is one or more units independently chosen from:

i) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl;
ii) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkoxy; or
iii) halogen.

22. The process according to any of Claims 18 to 21, wherein the boronic acid in step (A) is chosen from 2-fluorophenylboronic acid, 3-fluorophenylboronic acid, 4-fluorophenylboronic acid, 2-chlorophenylboronic acid, 3-chlorophenylboronic acid, 4-chlorophenylboronic acid, 2-methylphenylboronic acid, 3-methylphenylboronic acid, 4-methylphenylboronic acid, 2-methoxyphenylboronic acid, 3-methoxyphenylboronic acid, 4-methoxyphenylboronic acid, 2-cyanophenylboronic acid, 3-cyanophenylboronic acid, 4-cyanophenylboronic acid, 2-nitrophenylboronic acid, 3-nitrophenylboronic acid, 4-nitrophenylboronic acid, 2-trifluoromethylphenylboronic acid, 3-trifluoromethylphenylboronic acid, 4-trifluoromethylphenylboronic acid, 2-carbamoylphenylboronic acid, 3-carbamoylphenylboronic acid, 4-carbamoylphenylboronic acid, 2-(pyrrolidine-1-carbonyl)phenylboronic acid, 3-(pyrrolidine-1-carbonyl)phenylboronic acid, 4-(pyrrolidine-1-carbonyl)phenylboronic acid, 2-(cyclopropanecarbonylamino)phenylboronic acid, 3-(cyclopropanecarbonylamino)phenylboronic acid, and 4-(cyclopropanecarbonylamino)phenylboronic acid.

23. The process according to any of Claims 18 to 22, wherein the catalyst in step (A) is [1,1'-bis(diphenyphosphino)ferrocene]dichloro-palladium(II).

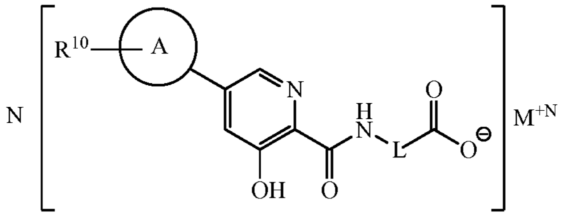
24. The process according to any of Claims 18 to 23, wherein the compound of step (D) is chosen from glycine, alanine, isoleucine, leucine, valine, 2-amino-2-methylpropanoic acid, 3-aminobutanoic acid, 3-amino-3-methylbutanoic acid, 3-amino-2-methylbutanoic acid, and 4-aminobutanoic acid.

25. The process according to any of Claims 18 to 23, wherein X is $-OR^3$ or $-NR^4R^5$ further comprising the step of hydrolyzing the compound formed in step (D) to form a compound wherein X is –OH.

26. The process according to Claim 25, wherein the hydrolysis is conducted in the presence of an acid catalyst.

27. The process according to Claim 25, wherein the hydrolysis is conducted in the presence of a base catalyst.

28. A compound having the formula:



wherein M is a salt forming cation and N represents the cationic charge on M;

A is a ring chosen from:

i) C_6 or C_{10} aryl; or

ii) C_1-C_9 heteroaryl;

R^{10} units represent at least one optionally present substitutions for a ring hydrogen atom; or two R^{10} units can be taken together to form a substituted or unsubstituted C_4-C_8 cycloalkyl ring, a substituted or unsubstituted C_6 or C_{10} aryl ring, a substituted or unsubstituted C_2-C_8 heterocyclic ring, or a substituted or unsubstituted C_3 to C_5 heteroaryl ring, wherein the heterocyclic and heteroaryl rings comprise one or more hetero atoms independently chosen from oxygen (O), nitrogen (N), or sulfur (S).

L is a linking unit having the formula:

$$-(CR^{7a}R^{7b})_n-$$

R^{7a} and R^{7b} are each independently:

i) hydrogen; or

ii) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl;

R^8 is chosen from hydrogen, methyl, or ethyl; and

the index n is an integer from 1 to 4.

29. The compound according to Claim 28, wherein A is a C_6 aryl ring.

30. The compound according to either Claim 28 or 29, wherein A is substituted by one or more R^{10} units independently chosen from:

i) C_1-C_{12} linear, C_3-C_{12} branched, or C_3-C_{12} cyclic alkyl, alkenyl, and alkynyl;

ii) C_6 or C_{10} aryl;

iii) C_7 or C_{11} alkylenearyl;

iv) C_1-C_9 heterocyclic rings;

- v) C_1-C_9 heteroaryl rings;
- vi) $-(CR^{102a}R^{102b})_aOR^{101}$;
- vii) $-(CR^{102a}R^{102b})_aC(O)R^{101}$;
- viii) $-(CR^{102a}R^{102b})_aC(O)OR^{101}$;
- ix) $-(CR^{102a}R^{102b})_aC(O)N(R^{101})_2$;
- x) $-(CR^{102a}R^{102b})_aN(R^{101})\,C(O)R^{101}$;
- xi) $-(CR^{102a}R^{102b})_aN(R^{101})\,C(O)_2R^{101}$;
- xii) $-(CR^{102a}R^{102b})_aN(R^{101})_2$;
- xiii) halogen;
- xiv) $-(CR^{102a}R^{102b})_I$;
- xv) $-(CR^{102a}R^{102b})_aNO_2$;
- xvi) $-(CH_{j'}X_{k'})_aCH_jX_k$; wherein X is halogen, the index j is an integer from 0 to 2, j + k = 3; the index j' is an integer from 0 to 2, j' + k' = 2;
- xvii) $-(CR^{102a}R^{102b})_aSR^{101}$;
- xviii) $-(CR^{102a}R^{102b})_aSO_2R^{101}$; and
- xix) $-(CR^{102a}R^{102b})_aSO_3R^{101}$;

wherein each R^{101} is independently hydrogen, substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl, phenyl, benzyl, heterocyclic, or heteroaryl; or two R^{101} units can be taken together to form a ring comprising 3-7 atoms; R^{102a} and R^{102b} are each independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl; the index "a" is from 0 to 4.

31. The compound according to any of Claims 28 to 30, wherein A is substituted by one or more R^{10} units independently chosen from:
- i) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkyl;
- ii) C_1-C_{12} linear, C_3-C_{12} branched or C_3-C_{12} cyclic alkoxy; or
- iii) halogen.

32. The compound according to any of Claims 28 to 31, wherein ring A is chosen from 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 3,5-dichlorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 2,4-dichlorophenyl,

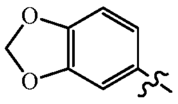
2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,3,6-trichlorophenyl, 2,4,5-trichlorophenyl, 3,4,5-trichlorophenyl, and 2,4,6-trichlorophenyl.

33. The compound according to any of Claims 28 to 31, wherein ring A is chosen from 2-chloro-3-methylphenyl, 2-chloro-4-methylphenyl, 2-chloro-5-methylphenyl, 2-chloro-6-methylphenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 3-chloro-5-methylphenyl, 3-chloro-6-methyl-phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluoro-5-methylphenyl, 2-fluoro-6-methylphenyl, 3-fluoro-2-methylphenyl, 3-fluoro-4-methylphenyl, 3-fluoro-5-methylphenyl, and 3-fluoro-6-methylphenyl.

34. The compound according to any of Claims 28 to 31, wherein ring A is chosen from 3-chlorophenyl, 3-fluorophenyl, 3-trifluoromethylphenyl, and 3-chloro-6-methylphenyl.

35. The compound according to Claim 28, wherein two R^{10} units are be taken together to form a substituted or unsubstituted C_2-C_8 heterocyclic ring, wherein the heterocyclic ring comprises one or more hetero atoms independently chosen from oxygen (O), nitrogen (N), or sulfur (S).

36. The compound according to either Claim 28 or 35, wherein two R^{10} units are taken together to form an A ring that has a formula chosen from:



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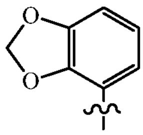

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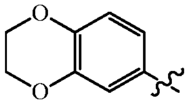
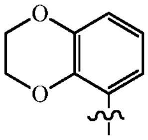


or



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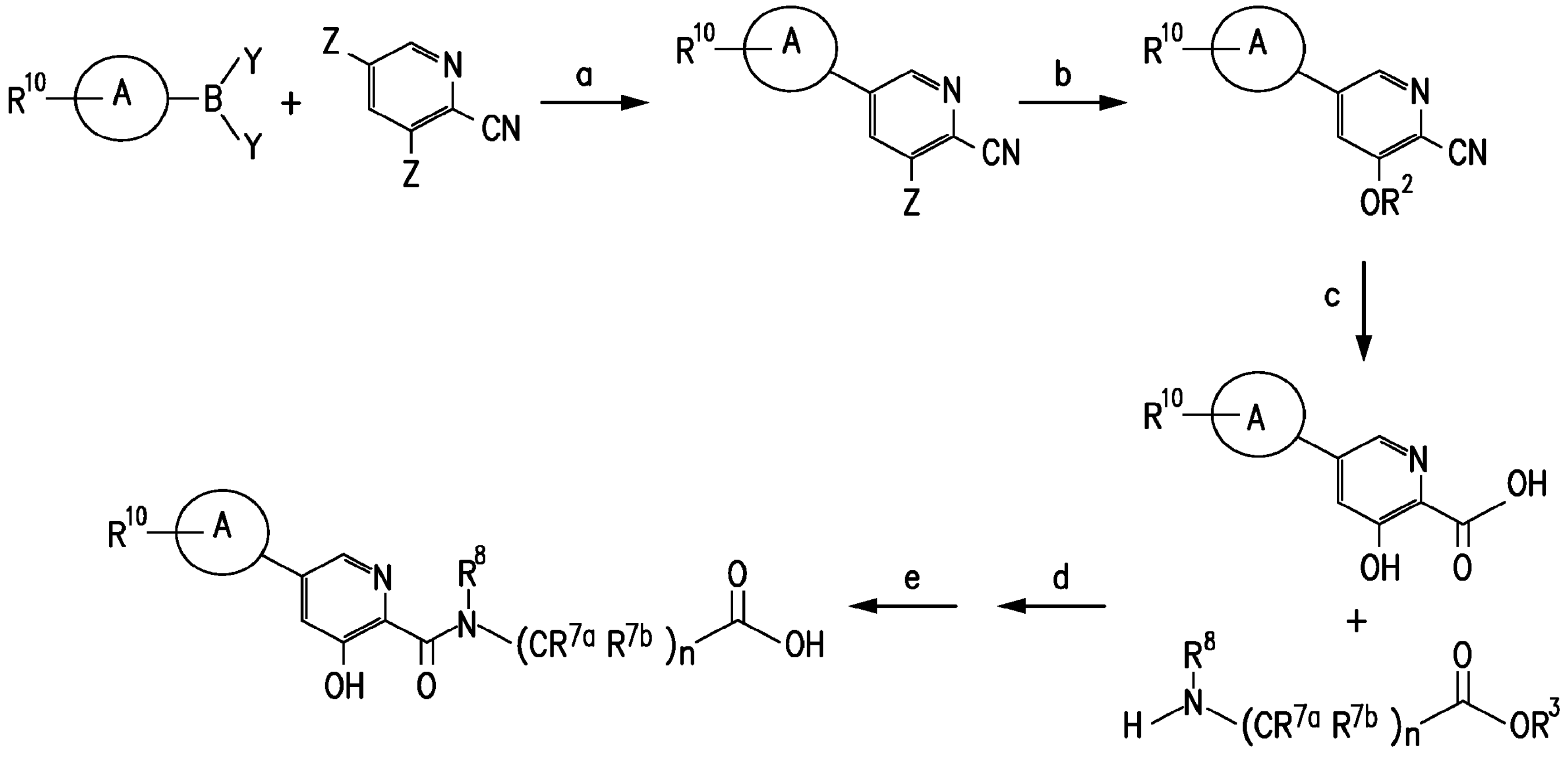
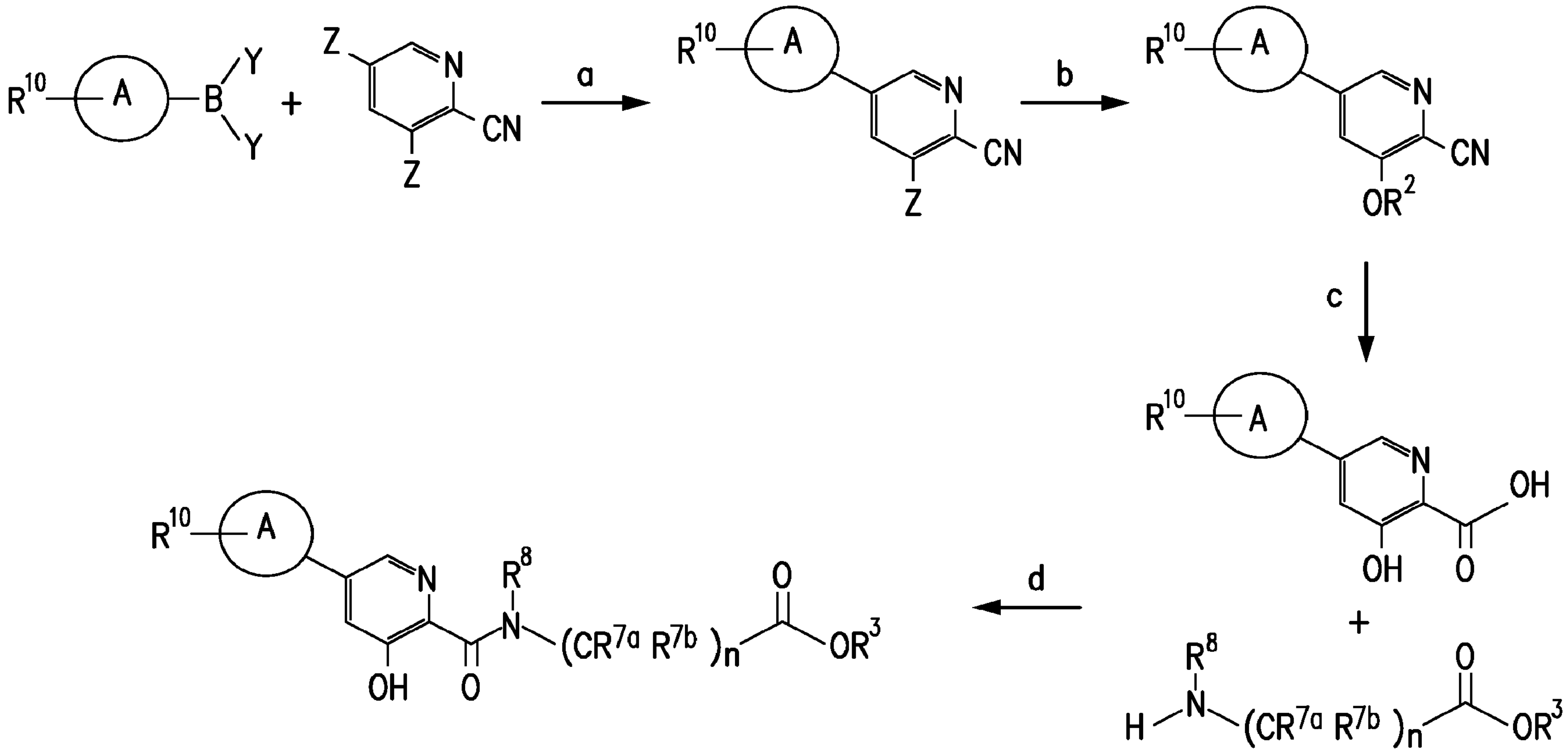


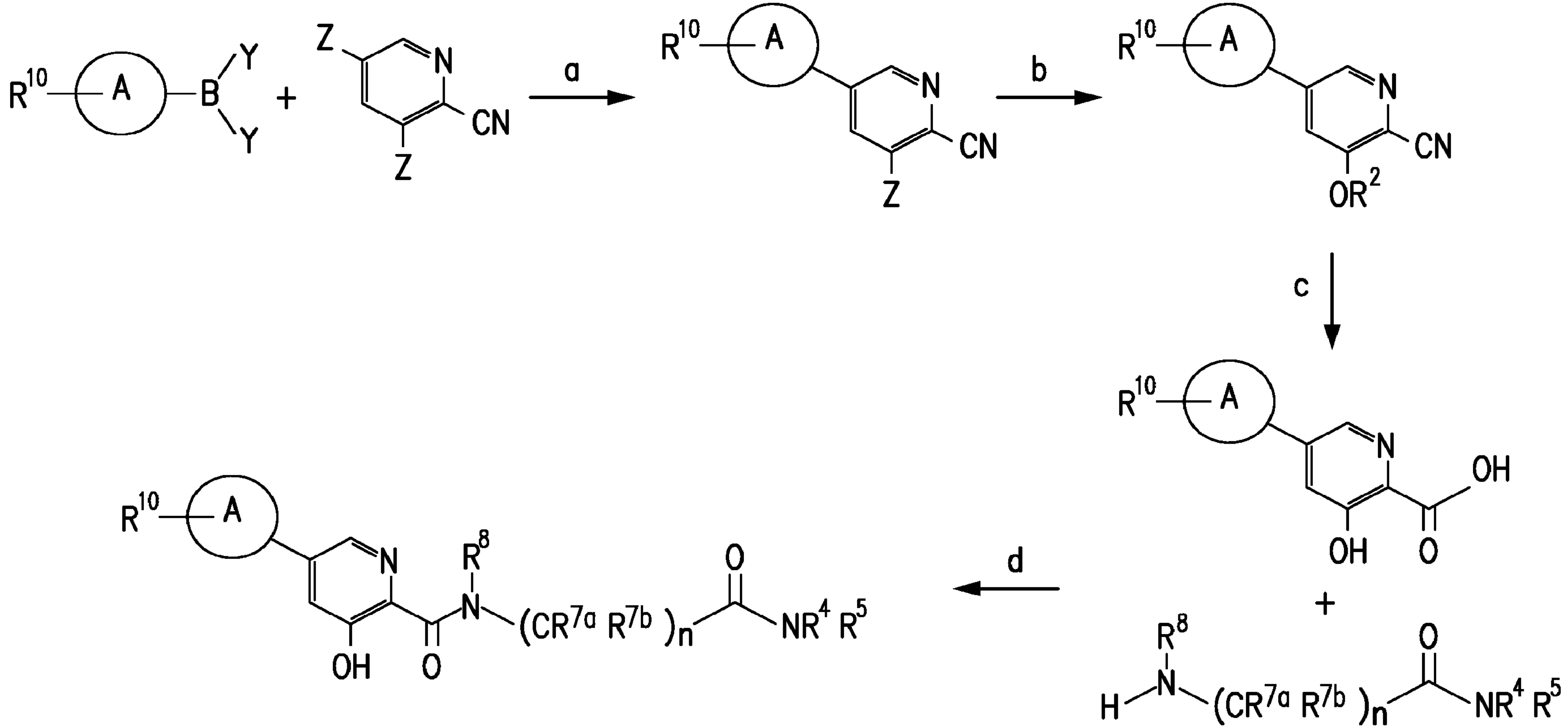
a) K_2CO_3, $PdCl_2$(dppf), DMF; b) $NaOCH_3$, CH_3OH; c) HCl, d) pivalolyl chloride, THF; e) NaOH

FIG. 1



a) K_2CO_3, $PdCl_2$(dppf), DMF; b) $NaOCH_3$, CH_3OH; c) HCl, d) pivalolyl chloride, THF

FIG. 2



a) K_2CO_3, $PdCl_2$(dppf), DMF; b) $NaOCH_3$, CH_3OH; c) HCl, d) pivalolyl chloride, THF

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/40833

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 213/62 (2012.01)
USPC - 546/298
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07D 213/62 (2012.01)
USPC: 546/298

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 546/296 (text search) Find search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar, SureChem (structure search)
pyridine carboxamide, $phenylpyridine, $arylpyridine, $cyanopyridine, $picolinonitrile, $carboxypyridine, $picolinic, proplyl hydroxylase, 3-hydroxy-5-phenyl-pyridine-2-carboxylic acid, suzuki, reaction, coupling

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 3,703,582 A (SHEN et al.) 21 November 1972 (21.11.1972) col 1, ln 65-70; col 11, ln 60-67; col 12, ln 1-15; col 28, ln 23-39, Table 1	1-3, 8-9 —— 10-12, 18-20
X — Y	US 2007/0299086 A1 (KAWAMOTO) 27 December 2007 (27.12.2007) para [0002], [0060]-[0065], [0085], [0108], [0155]-[0158], [0163], [0202], [0223]	28-30, 35-36 —— 10-12, 18-20
Y	WO 2009/111337 A1 (WU et al.) 11 September 2009 (11.09.2009) para [0177]-[0178], [0523] This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	10-12, 18-20
Y	US 2010/0021423 A1 (BRAMELD et al.) 28 January 2010 (28.01.2010) para [0213]-[0214]	10-12, 18-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 30 July 2012 (30.07.2012)	Date of mailing of the international search report 29 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-7, 13-17, 21-27 and 31-34
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.