METHOD FOR 1*H*-IMIDAZO[4,5-*c*]PYRIDINES AND ANALOGS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial No. 60/720171, filed on September 23, 2005, and U.S. Provisional Application Serial No. 60/743505, filed on March 16, 2006, both of which are incorporated herein by reference.

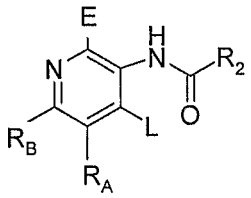
BACKGROUND

Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms. Thus, there is a need for methods and intermediates for making such compounds.

SUMMARY

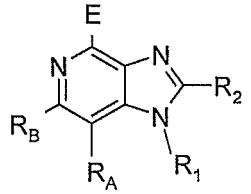
It has now been found that certain 1*H*-imidazo[4,5-*c*]pyridines and analogs thereof, or pharmaceutically acceptable salts thereof, can be prepared by a method comprising:

providing a compound of the Formula IV:



IV;

and reacting the compound of Formula IV with an amine of the formula R_1NH_2 to provide a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:

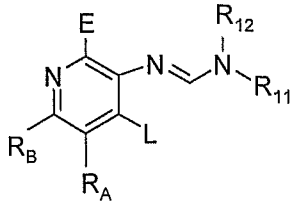


I

or a pharmaceutically acceptable salt thereof; wherein E, L, R_1, R_2, R_A, and R_B are defined below.

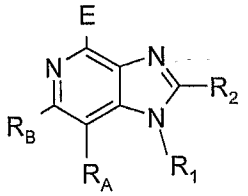
In another embodiment, certain 1*H*-imidazo[4,5-*c*]pyridines and analogs thereof, or pharmaceutically acceptable salts thereof, can be prepared by a method comprising:

providing a compound of the Formula VIII:



VIII

and reacting the compound of Formula VIII with an amine of the formula R_1NH_2 to provide a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:

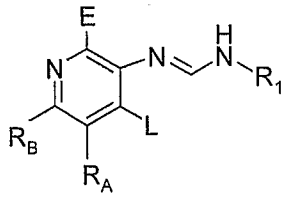


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or a pharmaceutically acceptable salt thereof; wherein E, L, R_1, R_2, R_{11}, R_{12}, R_A, and R_B are defined below.

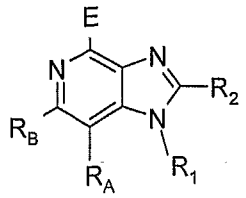
In another embodiment, certain 1*H*-imidazo[4,5-*c*]pyridines and analogs thereof, or pharmaceutically acceptable salts thereof, can be prepared by a method comprising:

providing a compound of the Formula XI:



XI

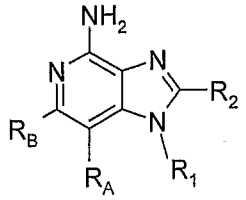
and forming a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:



I

or a pharmaceutically acceptable salt thereof; wherein E, L, R_1, R_2, R_A, and R_B are defined below.

Compounds and salts of Formula I are useful for making immune response modifying compounds of the following Formula X:

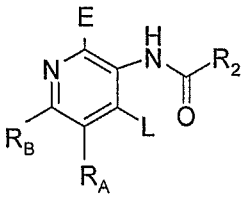


X

or pharmaceutically acceptable salts thereof; wherein R_1, R_2, R_A, and R_B are defined below. The compounds and salts of Formula X are known to be useful as immune response modifiers due to their ability to induce or inhibit cytokine biosynthesis (e.g., induces or inhibits the biosynthesis of at least one cytokine) and otherwise modulate the immune response when administered to animals. This makes these compounds and salts useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

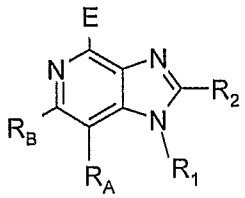
In one embodiment, there is provided a method that includes:

providing a compound of the Formula IV:



IV;

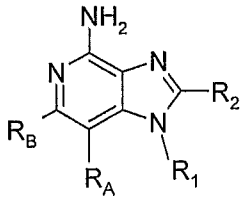
reacting the compound of Formula IV with an amine of the formula R_1NH_2 to provide a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:



I

or a pharmaceutically acceptable salt thereof; and

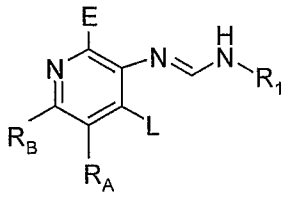
converting E to an amino group in the compound of Formula I to provide a compound (a 1*H*-imidazo[4,5-*c*]pyridin-4-amine or analog thereof) of the Formula X:



X

or a pharmaceutically acceptable salt thereof; wherein E, L, R_1, R_2, R_A, and R_B are defined below.

In another aspect, the invention provides intermediates useful in the preparation of immune response modifiers. In one embodiment, there is provided a compound of the Formula XI:



XI

wherein E, L, R_1, R_A, and R_B are defined below.

As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably.

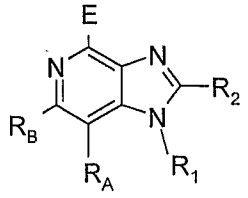
The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which

examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

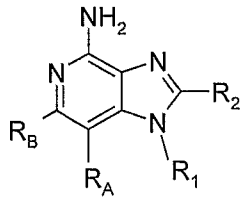
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides methods and intermediates for preparing certain 1*H*-imidazo[4,5-*c*]pyridines and analogs thereof of the Formula I:



I

or pharmaceutically acceptable salts thereof; which are useful for preparing compounds (1*H*-imidazo[4,5-*c*]pyridin-4-amines or analog thereof) of the Formula X:

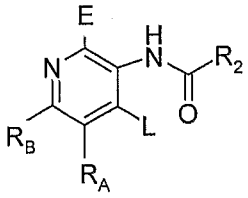


X

or pharmaceutically acceptable salts thereof; wherein E, R_1, R_2, R_A, and R_B are defined below.

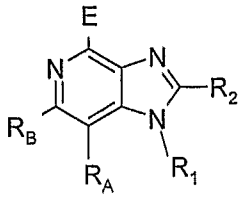
In one embodiment, there is provided a method (i) comprising:

providing a compound of the Formula IV:



IV

and reacting the compound of Formula IV with an amine of the formula R_1NH_2 to provide a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:



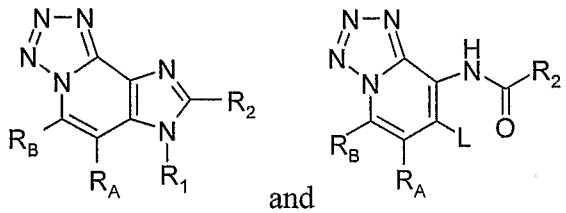
I

or a pharmaceutically acceptable salt thereof;

wherein:

E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formulas I and IV to form the fused tetrazolo ring in Formulas I-1 and IV-1:



I-1 and IV-1;

L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$,

$-X-R_5$,

$-N(R_1')-Q-R_4$,

$-N(R_1')-X_1-Y_1-R_4$, and

$-N(R_1')-X_1-R_{5b}$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

-Z-X-Y-R_4,

-Z-X-Y-X-Y-R_4, and

-Z-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X_1 is C_{2-20} alkylene;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-$N(R_8)$-Q-,

-O-$C(R_6)$-$N(R_8)$-,

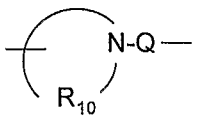
-$C(R_6)$-$N(OR_9)$-,

-O-$N(R_8)$-Q-,

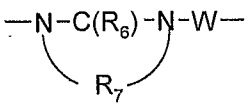
-O-N=$C(R_4)$-,

-C(=N-O-R_8)-,

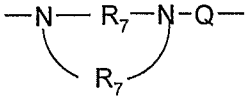
-CH(-N(-O-R_8)-Q-R_4)-,



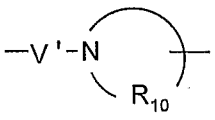
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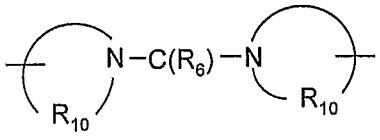
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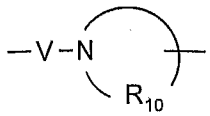


, and



;

Y_1 is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-,



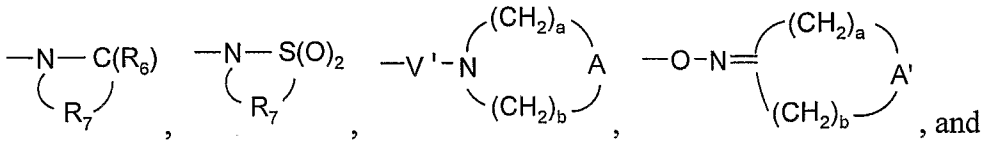
-N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, and ;

Z is a bond or -O-;

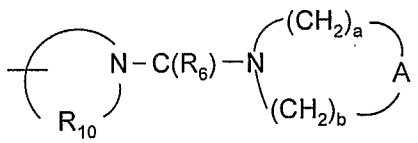
R_1' is selected from the group consisting of hydrogen, C_{1-20} alkyl, hydroxy-C_{2-20} alkylenyl, and alkoxy-C_{2-20} alkylenyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

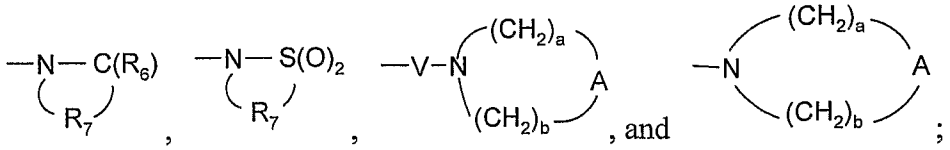


, and



;

R_{5b} is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

V' is selected from the group consisting of $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

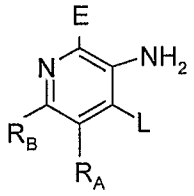
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

This ring forming reaction is unexpected, since the L group is displaced without a strong electron withdrawing group adjacent the L group.

In another embodiment, there is provided a method (ii) wherein the above method (i) further comprises the steps of:

providing a compound of the Formula III:

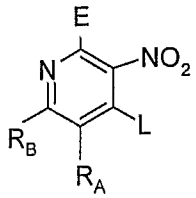


III

and reacting the compound of Formula III with a carboxylic acid halide of the formula hal-C(O)-R_2, wherein hal is chloro or bromo, or an anhydride or mixed anhydride of the formula $O(-C(O)-R_2)_2$ to provide an compound of Formula IV.

In another embodiment, there is provided a method (iii) wherein the above method (ii) further comprises the steps of:

providing a compound of the Formula II:

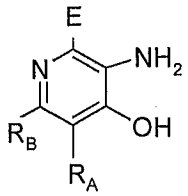


II

and reducing the compound of Formula II to provide a compound of Formula III.

In another embodiment, there is provided a method (iv) wherein the method (ii) further comprises the steps of:

providing a compound of the Formula VI:

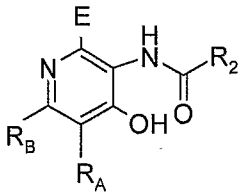


VI

and converting the hydroxy group at the 4-position of Formula VI to an L group to provide a compound of Formula III.

In another embodiment, there is provided a method (v) wherein the method (i) further comprises the steps of:

providing a compound of the Formula VII:

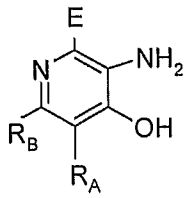


VII

and converting the hydroxy group at the 4-position of Formula VII to an L group to provide a compound of Formula IV.

In another embodiment, there is provided a method (vi) wherein the method (v) further comprises the steps of:

providing a compound of the Formula VI:

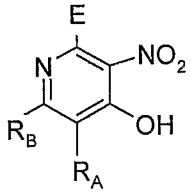


VI

and reacting the compound of Formula VI with a carboxylic acid halide of the formula hal-C(O)-R_2, wherein hal is a chloro or bromo, or an anhydride or mixed anhydride of the formula O(-C(O)-R_2)$_2$ to provide an compound of Formula VII.

In other embodiments, there is provided a method (vii) or (viii) wherein the method (iv) or (vi), respectively, further comprises the steps of:

providing a compound of the Formula V:

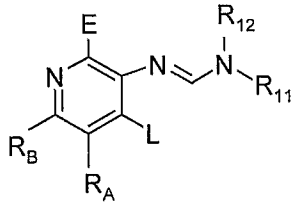


V

and reducing the compound of Formula V to provide a compound of Formula VI.

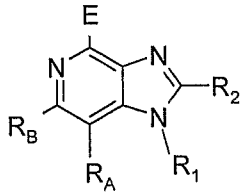
In one embodiment, there is provided a method (ix) that includes:

providing a compound of the Formula VIII:



VIII

and reacting the compound of Formula VIII with an amine of the formula R_1NH_2 to provide a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:



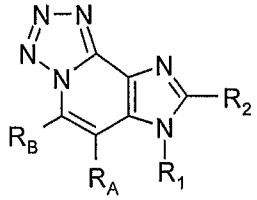
I

or a pharmaceutically acceptable salt thereof;

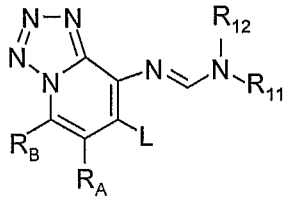
wherein:

E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formulas I and VIII to form the fused tetrazolo ring in Formulas I-1 and IX:



and



I-1 IX;

L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_1 is selected from the group consisting of:
$-R_4$,
$-X-R_4$,
$-X-Y-R_4$,
$-X-Y-X-Y-R_4$,
$-X-R_5$,
$-N(R_1')-Q-R_4$,
$-N(R_1')-X_1-Y_1-R_4$, and
$-N(R_1')-X_1-R_{5b}$;

R_2 is hydrogen;

R_3 is selected from the group consisting of:
$-Z-R_4$,
$-Z-X-R_4$,
$-Z-X-Y-R_4$,
$-Z-X-Y-X-Y-R_4$, and
$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X_1 is C_{2-20} alkylene;

Y is selected from the group consisting of:
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-O-C(R_6)-$,

$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-O-C(R_6)-N(R_8)-$,

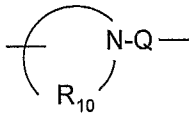
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

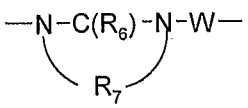
$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

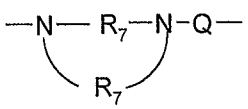
$-CH(-N(-O-R_8)-Q-R_4)-$,



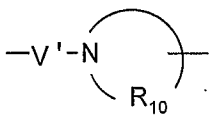
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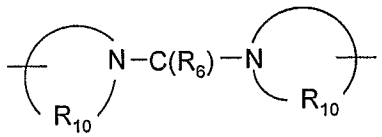
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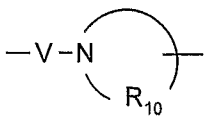


, and



;

Y_1 is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, and



;

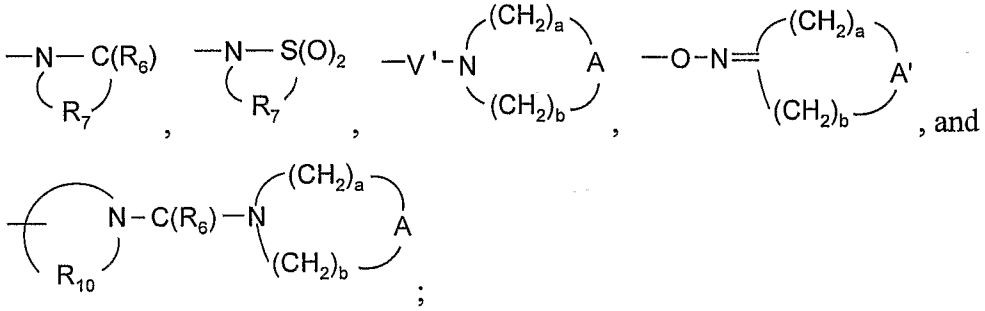
Z is a bond or -O-;

R_1' is selected from the group consisting of hydrogen, C_{1-20} alkyl, hydroxy-C_{2-20} alkylenyl, and alkoxy-C_{2-20} alkylenyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

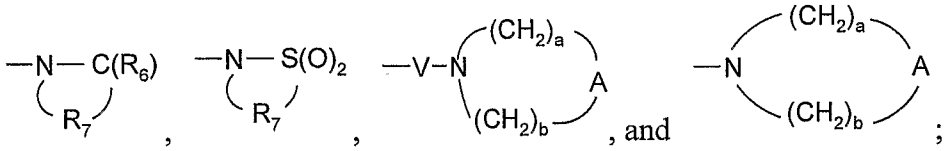
heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_{5b} is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} and R_{12} are independently C_{1-4} alkyl or R_{11} and R_{12} together with the nitrogen atom to which they are attached form a 5- or 6-membered ring optionally containing -O-, –N(C_{1-4} alkyl)-, or -S-;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, and –$N(R_4)$-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-,

-$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

V' is selected from the group consisting of -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

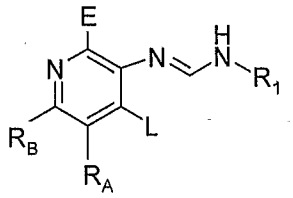
W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

This ring forming reaction is also unexpected, since the L group is displaced without a strong electron withdrawing group adjacent the L group.

In another embodiment, there is provided a method (x) wherein the above method (ix) further comprises:

forming an intermediate of Formula XI:



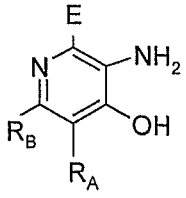
XI

after reacting the compound of Formula VIII with an amine of the formula R_1NH_2.

In another embodiment, there is provided a method (xi) wherein the intermediate of Formula XI in method (x) above is isolated after reacting the compound of Formula VIII with an amine of the formula R_1NH_2.

In other embodiments, there is provided a method (xii) or (xiii) wherein the above method (ix) or (x), respectively, further comprises:

providing a compound of the Formula VI:



VI

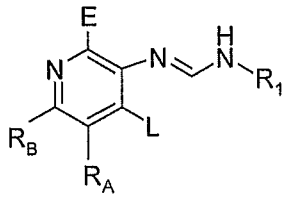
converting the hydroxy group at the 4-position to an L group,

and reacting the amino group at the 3-position with a formamide of the formula H-C(O)-$N(R_{11})R_{12}$ to provide a compound of Formula VIII.

In other embodiments, there is provided a method (xiv) or (xv) wherein the compound of Formula VIII in the above method (xii) or (xiii), respectively, is provided without being isolated prior to reacting with an amine of the formula R_1NH_2.

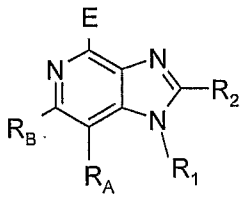
In one embodiment, there is provided a method (xvi) that includes:

providing a compound of the Formula XI:



XI

and forming a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:



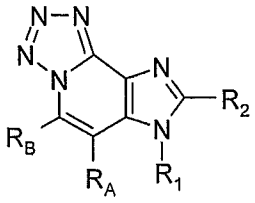
I

or a pharmaceutically acceptable salt thereof;

wherein:

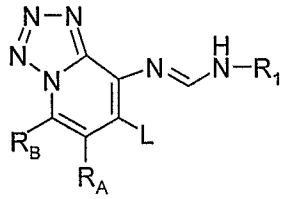
E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formulas I and XI to form the fused tetrazolo ring in Formulas I-1 and XIII:



I-1

and



XIII;

L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,
-X-R_4,
-X-Y-R_4,
-X-Y-X-Y-R_4,
-X-R_5,

$-N(R_1')-Q-R_4$,

$-N(R_1')-X_1-Y_1-R_4$, and

$-N(R_1')-X_1-R_{5b}$;

R_2 is hydrogen;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X_1 is C_{2-20} alkylene;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-O-C(R_6)-N(R_8)-$,

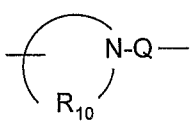
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

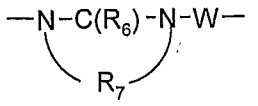
$-O-N=C(R_4)-$,

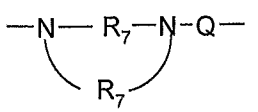
$-C(=N-O-R_8)-$,

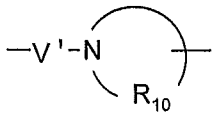
$-CH(-N(-O-R_8)-Q-R_4)-$,

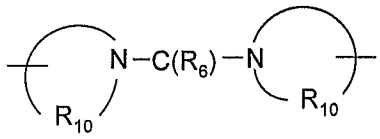


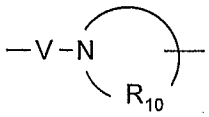
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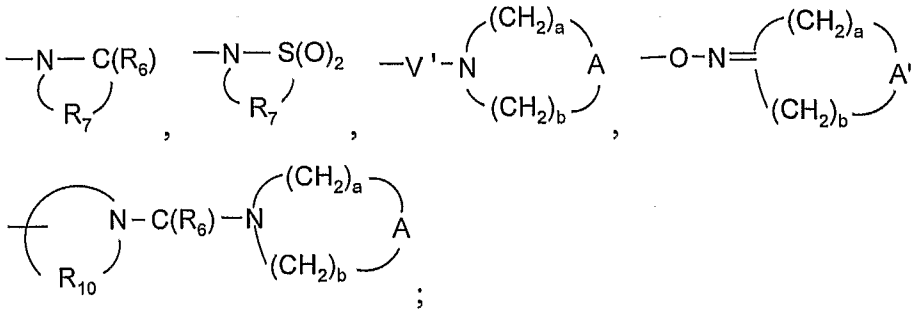
Y_1 is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, and 
;

Z is a bond or -O-;

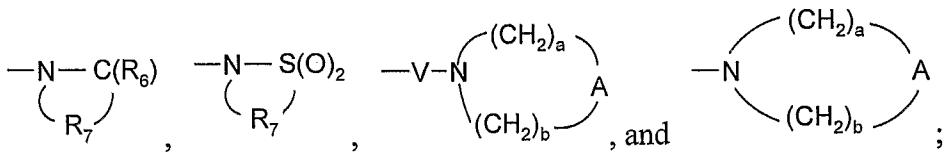
R_1' is selected from the group consisting of hydrogen, C_{1-20} alkyl, hydroxy-C_{2-20} alkylenyl, and alkoxy-C_{2-20} alkylenyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_{5b} is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

V' is selected from the group consisting of $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

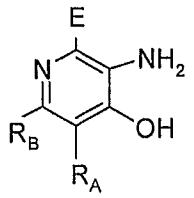
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$.

This ring forming reaction is also unexpected, since the L group is displaced without a strong electron withdrawing group adjacent the L group.

In another embodiment, there is provided a method (xvii) wherein the above method (xvi) further comprises:

providing a compound of the Formula VI:

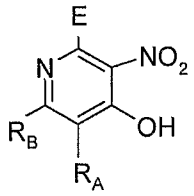


VI

converting the hydroxy group at the 4-position to an L group,
and reacting the amino group at the 3-position with a formamide of the formula
H-C(O)-NH(R_1) to provide a compound of Formula XI.

In another embodiment, there is provided a method (xviii) wherein the compound of Formula XI in the above method (xvii) is provided without being isolated prior to forming a compound of Formula I.

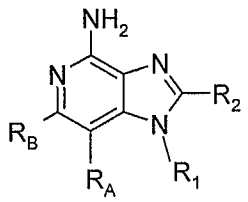
In other embodiments, there is provided a method (xix), (xx), (xxi), (xxii), (xxiii), or (xxiv) wherein the above method (xii), (xiii), (xiv), (xv), (xvii), or (xviii) further comprises providing a compound of the Formula V:



V

and reducing the compound of Formula V to provide a compound of Formula VI.

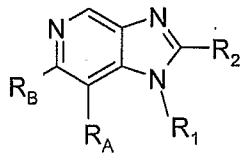
In other embodiments, there is provided a method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) wherein the method (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x), (xi), (xii), (xiii), (xiv), (xv), (xvi), (xvii), (xviii), (xix), (xx), (xxi), (xxii), (xxiii), or (xxiv), respectively, further comprises the step of converting E to an amino group in the compound of Formula I to provide a compound of the Formula X:



X,

or a pharmaceutically acceptable salt thereof.

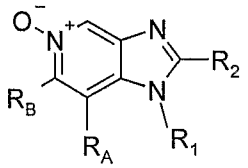
In other embodiments, there is provided a method (i-2), (ii-2), (iii-2), (iv-2), (v-2), (vi-2), (vii-2), (viii-2), (ix-2), (x-2), (xi-2), (xii-2), (xiii-2), (xiv-2), (xv-2), (xvi-2), (xvii-2), (xviii-2), (xix-2), (xx-2), (xxi-2), (xxii-2), (xxiii-2), or (xxiv-2) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) is hydrogen, the compound of Formula I is the Formula I-2:



I-2,

and the step of converting the hydrogen to an amino group in the compound of Formula I-2 comprises:

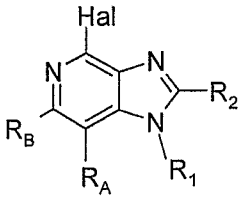
oxidizing the compound of Formula I-2 to provide a the 5*N*-oxide of Formula XX:



XX,

and aminating the compound of Formula XX to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

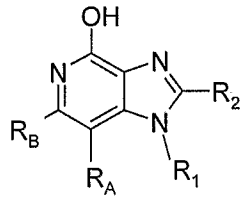
In other embodiments, there is provided a method (i-3), (ii-3), (iii-3), (iv-3), (v-3), (vi-3), (vii-3), (viii-3), (ix-3), (x-3), (xi-3), (xii-3), (xiii-3), (xiv-3), (xv-3), (xvi-3), (xvii-3), (xviii-3), (xix-3), (xx-3), (xxi-3), (xxii-3), (xxiii-3), or (xxiv-3) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) is Hal, the compound of Formula I is the Formula I-3:



I-3

wherein Hal is fluoro, chloro, bromo, or iodo, and the step of converting the Hal group to an amino group in the compound of Formula I-3 comprises aminating the compound of Formula I-3 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

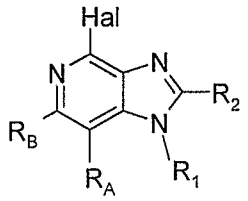
In other embodiments, there is provided a method (i-4), (ii-4), (iii-4), (iv-4), (v-4), (vi-4), (vii-4), (viii-4), (ix-4), (x-4), (xi-4), (xii-4), (xiii-4), (xiv-4), (xv-4), (xvi-4), (xvii-4), (xviii-4), (xix-4), (xx-4), (xxi-4), (xxii-4), (xxiii-4), or (xxiv-4) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) is hydroxy, the compound of Formula I is the Formula I-4:



I-4,

and the step of converting the hydroxy group to an amino group in the compound of Formula I-4 comprises:

converting the hydroxy group at the 4-position of Formula I-4 to a halo group to provide a compound or salt of Formula I-3:



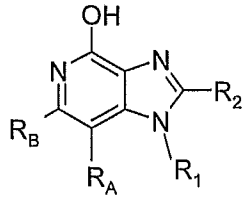
I-3

wherein Hal is fluoro, chloro, bromo, or iodo; and

aminating the compound of Formula I-3 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

In other embodiments, there is provided a method (i-5), (ii-5), (iii-5), (iv-5), (v-5), (vi-5), (vii-5), (viii-5), (ix-5), (x-5), (xi-5), (xii-5), (xiii-5), (xiv-5), (xv-5), (xvi-5), (xvii-5), (xviii-5), (xix-5), (xx-5), (xxi-5), (xxii-5), (xxiii-5), or (xxiv-5) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1),

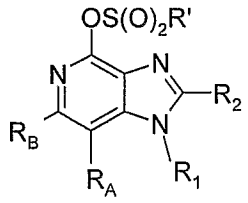
(xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) is hydroxy, the compound of Formula I is the Formula I-4:



I-4,

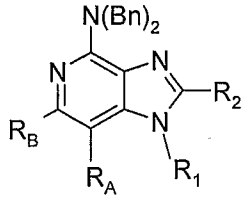
and the step of converting the hydroxy group to an amino group in the compound of Formula I-4 comprises:

sulfonating the compound of Formula I-4 by reaction with a compound of the formula hal-$S(O)_2$-R' wherein hal is chloro or bromo, or the formula $O(-S(O)_2-R')_2$, to provide a compound of the Formula I-5:



I-5

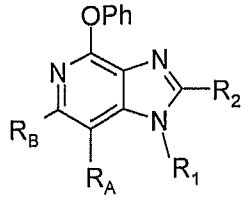
displacing the -O-$S(O)_2$-R' group in Formula I-5 by an amino group of the formula -$N(Bn)_2$ to provide a compound of the Formula I-6:



I-6

removing the Bn protecting groups in Formula I-6 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

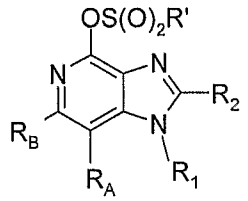
In other embodiments, there is provided a method (i-6), (ii-6), (iii-6), (iv-6), (v-6), (vi-6), (vii-6), (viii-6), (ix-6), (x-6), (xi-6), (xii-6), (xiii-6), (xiv-6), (xv-6), (xvi-6), (xvii-6), (xviii-6), (xix-6), (xx-6), (xxi-6), (xxii-6), (xxiii-6), or (xxiv-6) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) is phenoxy, the compound of Formula I is the Formula I-7:



I-7,

wherein Ph is phenyl, and the step of converting the phenoxy group to an amino group in the compound of Formula I-7 comprises aminating the compound of Formula I-7 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

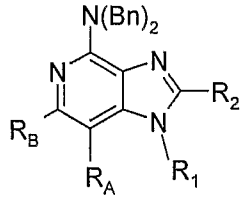
In other embodiments, there is provided a method (i-7), (ii-7), (iii-7), (iv-7), (v-7), (vi-7), (vii-7), (viii-7), (ix-7), (x-7), (xi-7), (xii-7), (xiii-7), (xiv-7), (xv-7), (xvi-7), (xvii-7), (xviii-7), (xix-7), (xx-7), (xxi-7), (xxii-7), (xxiii-7), or (xxiv-7) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxxiv-1) is $-O-S(O)_2-R'$, the compound of Formula I is the Formula I-5:



I-5,

and the step of converting the $-O-S(O)_2-R'$ group to an amino group in the compound of Formula I-5 comprises:

displacing the $-O-S(O)_2-R'$ group by an amino group of the formula $-N(Bn)_2$ to provide a compound of the Formula I-6:

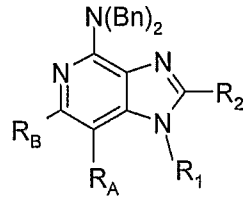


I-6

and removing the Bn protecting groups in Formula I-6 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

In other embodiments, there is provided a method (i-8), (ii-8), (iii-8), (iv-8), (v-8), (vi-8), (vii-8), (viii-8), (ix-8), (x-8), (xi-8), (xii-8), (xiii-8), (xiv-8), (xv-8), (xvi-8), (xvii-

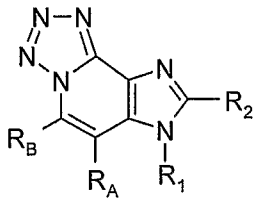
8), (xviii-8), (xix-8), (xx-8), (xxi-8), (xxii-8), (xxiii-8), or (xxiv-8) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) is $-N(Bn)_2$, the compound of Formula I is the Formula I-6:



I-6,

and the step of converting the $-N(Bn)_2$ group to an amino group in the compound of Formula I-6 comprises removing the Bn protecting groups to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

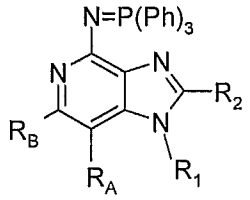
In other embodiments, there is provided a method (i-9), (ii-9), (iii-9), (iv-9), (v-9), (vi-9), (vii-9), (viii-9), (ix-9), (x-9), (xi-9), (xii-9), (xiii-9), (xiv-9), (xv-9), (xvi-9), (xvii-9), (xviii-9), (xix-9), (xx-9), (xxi-9), (xxii-9), (xxiii-9), or (xxiv-9) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) is joined with the adjacent pyridine nitrogen atom of Formula I to form the fused tetrazolo ring in Formula I-1:



I-1,

and the step of converting the fused tetrazolo ring to an amino group in the compound of Formula I-1 comprises the steps of:

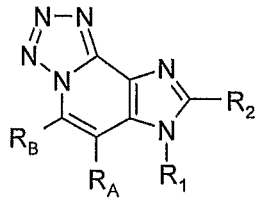
reacting the compound of Formula I-1 with triphenylphosphine to provide a compound of the Formula XXI:



XXI

and hydrolyzing the compound of Formula XXI to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

In other embodiments, there is provided a method (i-10), (ii-10), (iii-10), (iv-10), (v-10), (vi-10), (vii-10), (viii-10), (ix-10), (x-10), (xi-10), (xii-10), (xiii-10), (xiv-10), (xv-10), (xvi-10), (xvii-10), (xviii-10), (xix-10), (xx-10), (xxi-10), (xxii-10), (xxiii-10), or (xxiv-10) wherein E in the method (i-1), (ii-1), (iii-1), (iv-1), (v-1), (vi-1), (vii-1), (viii-1), (ix-1), (x-1), (xi-1), (xii-1), (xiii-1), (xiv-1), (xv-1), (xvi-1), (xvii-1), (xviii-1), (xix-1), (xx-1), (xxi-1), (xxii-1), (xxiii-1), or (xxiv-1) is joined with the adjacent pyridine nitrogen atom of Formula I to form the fused tetrazolo ring in Formula I-1:

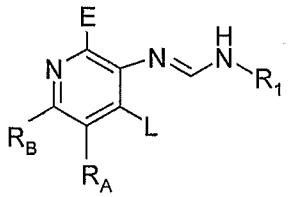


I-1,

and the step of converting the fused tetrazolo ring to an amino group in the compound of Formula I-1 comprises the step of:

reductively removing the tetrazolo ring from the compound of Formula I-1 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention provides an intermediate compound of Formula XI:

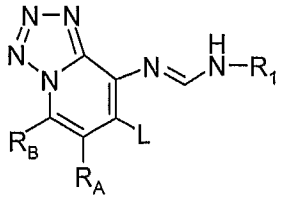


XI

wherein:

E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formula XI to form the fused tetrazolo ring in Formula XIII:



XIII;

L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$,

$-X-R_5$,

$-N(R_1')-Q-R_4$,

$-N(R_1')-X_1-Y_1-R_4$, and

$-N(R_1')-X_1-R_{5b}$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X_1 is C_{2-20} alkylene;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-O-C(R_6)-N(R_8)-$,

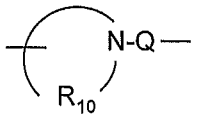
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

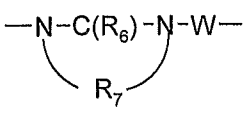
-O-N=C(R_4)-,

-C(=N-O-R_8)-,

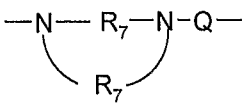
-CH(-N(-O-R_8)-Q-R_4)-,



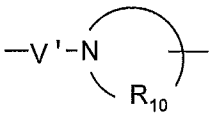
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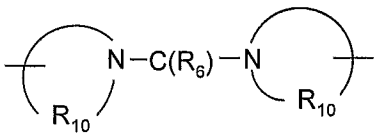
,



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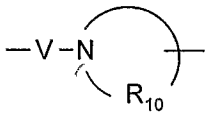


, and



;

Y_1 is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-,



-N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, and ;

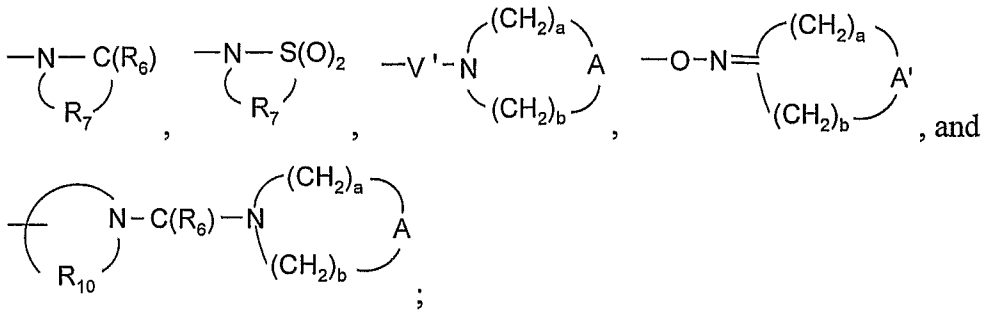
Z is a bond or -O-;

R_1' is selected from the group consisting of hydrogen, C_{1-20} alkyl, hydroxy-C_{2-20} alkylenyl, and alkoxy-C_{2-20} alkylenyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

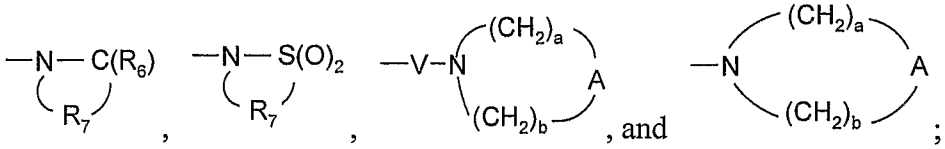
R_5 is selected from the group consisting of:



, and

;

R_{5b} is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, and –$N(R_4)$-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

V' is selected from the group consisting of -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

For certain embodiments, including any one of the above embodiments, R_1 is selected from the group consisting of -R_4, -X-R_4, -X-Y-R_4, -X-Y-X-Y-R_4, -X-R_5, -N(R_1')-Q-R_4, -N(R_1')-X_1-Y_1-R_4, and -N(R_1')-X_1-R_{5b}.

For certain embodiments, including any one of the above embodiments, R_1 is selected from the group consisting of -R_4, -X-R_4, -X-Y-R_4, -X-Y-X-Y-R_4, and -X-R_5.

For certain embodiments, including any one of the above embodiments, R_1 is -R_4 or -X-R_4. For certain of these embodiments, -R_4 is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,2-dimethyl-4-oxopentyl, and (1-hydroxycyclobutyl)methyl. For certain of these embodiments, R_1 is -R_4, and -R_4 is 2-methylpropyl or 2-hydroxy-2-methylpropyl. For certain of these embodiments, R_1 is -R_4, and -R_4 is 2-methylpropyl. Alternatively, for certain of these embodiments, R_1 is -X-R_4, and -X-R_4 is 2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl.

For certain embodiments, including any one of the above embodiments except for embodiments where R_1 is -R_4 or -X-R_4, R_1 is -X-Y-R_4. For certain of these embodiments, X is C_{2-4} alkylene, and Y is -$S(O)_2$- or -$N(R_8)$-Q-. For certain of these embodiments, -X-Y-R_4 is selected from the group consisting of 2-(propylsulfonyl)ethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 4-methylsulfonylaminobutyl, and 2-(acetylamino)-2-methylpropyl.

For certain embodiments, including any one of the above embodiments except for embodiments where R_1 is -R_4, -X-R_4, or -X-Y-R_4, R_1 is -X-R_5. For certain of these embodiments, -X-R_5 is 4-[(morpholin-4-ylcarbonyl)amino]butyl.

For certain embodiments, including any one of the above embodiments except for embodiments where R_1 is -R_4, -X-R_4, -X-Y-R_4, -X-Y-X-Y-R_4, or -X-R_5, R_1 is selected from the group consisting of -$N(R_1')$-Q-R_4, -$N(R_1')$-X_1-Y_1-R_4, and -$N(R_1')$-X_1-R_{5b}.

For certain embodiments, including any one of the above embodiments except for embodiments where R_2 is hydrogen, R_2 is selected from the group consisting of -R_4, -X-R_4, -X-Y-R_4, and -X-R_5.

For certain embodiments, including any one of the above embodiments except for embodiments where excluded, R_2 is -R_4. For certain of these embodiments, R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, ethoxymethyl, and hydroxymethyl. For certain of these embodiments, R_2 is selected from the group consisting of hydrogen, methyl, ethyl, and ethoxymethyl. For certain embodiments, R_2 is hydrogen.

For certain embodiments, including any one of the above embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups.

For certain embodiments, including any one of the above embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain of these embodiments, R_A and R_B are each methyl.

For certain embodiments, including any one of the above embodiments where R_A and R_B taken together can form a fused benzene ring, R_A and R_B taken together form a fused benzene ring wherein the benzene ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group. For certain of these embodiments, R is hydroxy or bromo, and R_3 is methoxy, phenoxy, or benzyloxy. For certain of these embodiments, the fused benzene ring is substituted by one R group selected from the group consisting of hydroxy and bromo. Alternatively, for certain of these embodiments, the fused benzene ring is substituted by one R_3 group wherein R_3 is methoxy, phenoxy, or benzyloxy. For certain embodiments, R_A and R_B taken together form a fused benzene ring wherein the benzene ring is unsubstituted.

For certain embodiments, including any one of the above embodiments where R_A and R_B taken together can form a fused pyridine ring, R_A and R_B taken together form a fused pyridine ring wherein the fused pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group; and wherein the fused pyridine ring is



, wherein the highlighted bond indicates the position where the ring is fused. For certain of these embodiments, R is hydroxy or bromo, and R_3 is methoxy, phenoxy, or benzyloxy. For certain of these embodiments, the fused pyridine ring is substituted by one

R group selected from the group consisting of hydroxy and bromo. Alternatively, for certain of these embodiments, the fused pyridine ring is substituted by one R_3 group wherein R_3 is methoxy, phenoxy, or benzyloxy. For certain embodiments, R_A and R_B taken together form a fused pyridine ring wherein the fused pyridine ring is unsubstituted, and wherein the fused pyridine ring is



, wherein the highlighted bond indicates the position where the ring is fused.

For certain embodiments, including any one of the above embodiments where R_A and R_B taken together can form a fused 5 to 7 membered saturated ring, R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups. For certain of these embodiments, R_A and R_B taken together form a fused 5 to 7 membered carbocyclic ring wherein the fused ring is unsubstituted or substituted by one or more R groups. For certain of these embodiments, the fused ring is a 6 membered carbocyclic ring which is unsubstituted. Alternatively, for certain of these embodiments, R_A and R_B taken together form a fused 5 to 7 membered saturated ring containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups. For certain of these embodiments, the fused ring is a fused 6 membered ring which is unsubstituted or substituted at a carbon atom by one or more R groups. For certain of these embodiments, the fused 6 membered ring is



wherein the ring is unsubstituted; and wherein the highlighted bond indicates the position where the ring is fused.

For certain embodiments, including any one of the above embodiments of methods (i) through (viii), methods (i-1) through (viii-1), methods (i-2) through (viii-2), methods (i-3) through (viii-3), methods (i-4) through (viii-4), methods (i-5) through (viii-5), methods (i-6) through (viii-6), methods (i-7) through (viii-7), methods (i-8) through (viii-8), methods (i-9) through (viii-9), and methods (i-10) through (viii-10), R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, wherein:

R_{A1} and R_{B1} are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_{A1} and R_{B1} taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R_a group, or substituted by one R_{3a} group, or substituted by one R_a group and one R_{3a} group;

or R_{A1} and R_{B1} taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R_a groups;

R_a is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
trifluoromethyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_{1a} is selected from the group consisting of:
$-R_{4a}$,
$-X-R_{4a}$,
$-X-Y_a-R_{4a}$,
$-X-Y_a-X-Y_a-R_{4a}$,
$-X-R_{5a}$,
$-N(R_1')-Q-R_{4a}$,
$-N(R_1')-X_1-Y_1-R_{4a}$, and
$-N(R_1')-X_1-R_{5b}$;

R_{2a} is selected from the group consisting of:
$-R_{4a}$,
$-X-R_{4a}$,

-X-Y_a-R_{4a}, and

-X-R_{5a};

R_{3a} is selected from the group consisting of:

-Z-R_{4a},

-Z-X-R_{4a},

-Z-X-Y_a-R_{4a},

-Z-X-Y_a-X-Y_a-R_{4a}, and

-Z-X-R_{5a};

Y_a is selected from the group consisting of:

-O-,

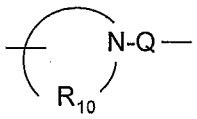
-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

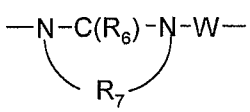
-$N(R_8)$-Q-,

-O-$C(R_6)$-$N(R_8)$-,

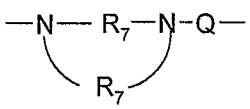
-$C(R_6)$-$N(OR_9)$-,



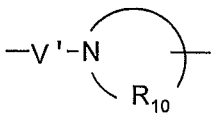
,



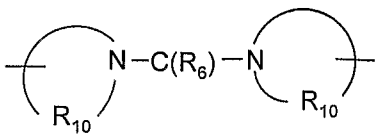
,



,



, and

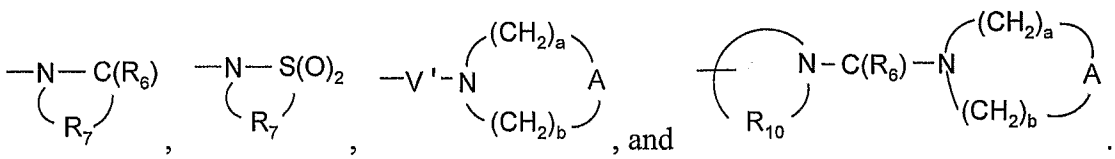


;

R_{4a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

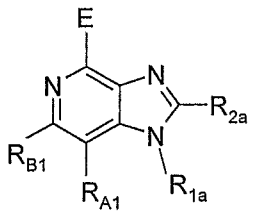
heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, trifluoromethoxy, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, and (dialkylamino)alkyleneoxy; and

R_{5a} is selected from the group consisting of:



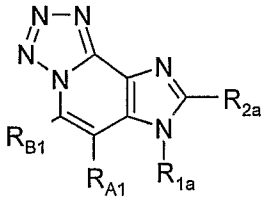
For each of the resulting embodiments, where present:

Formula I is Formula I_a:



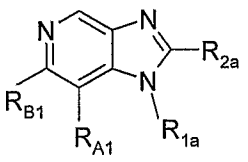
I_a,

Formula I-1 is Formula I_a-1:



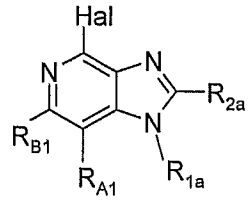
I_a-1,

Formula I-2 is Formula I_a-2:



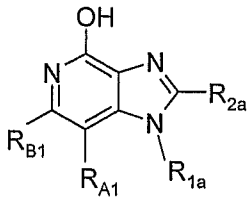
I_a-2,

Formula I-3 is Formula I_a-3:



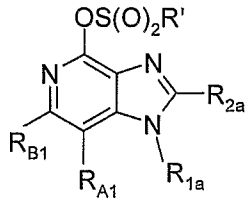
I_a-3,

Formula I-4 is Formula I_a-4:



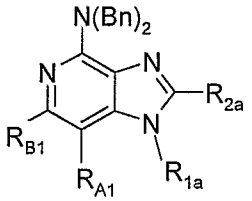
I_a-4,

Formula I-5 is I_a-5:



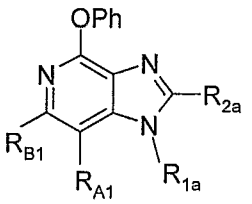
I_a-5,

Formula I-6 is I_a-6:



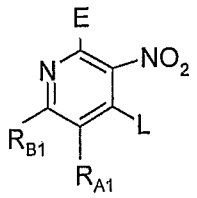
I_a-6

Formula I-7 is I_a-7:



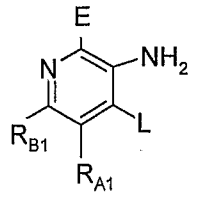
I_a-7

Formula II is Formula II_a:



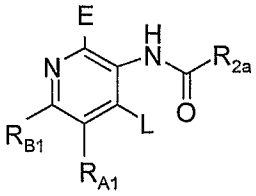
II_a,

Formula III is Formula III_a:



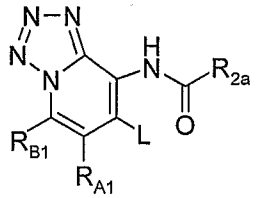
III_a,

Formula IV is Formula IV_a:



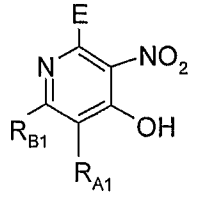
IV_a,

Formula IV-1 is Formula IV_a-1:



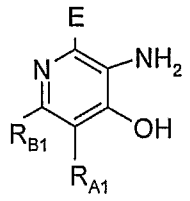
IV_a-1

Formula V is Formula V_a:



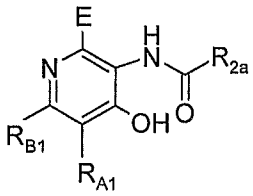
V_a,

Formula VI is Formula VI_a:



VI_a,

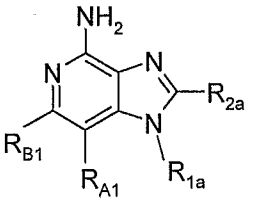
and Formula VII is Formula VII_a:



VII_a.

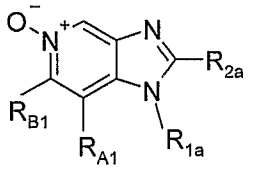
For certain of the resulting embodiments, where present:

Formula X is Formula X_a:



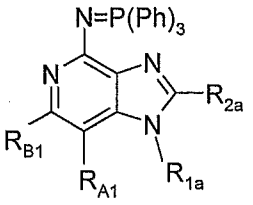
X_a,

Formula XX is Formula XX_a:



XX_a,

and Formula XXI is Formula XXI_a:



XXI_a.

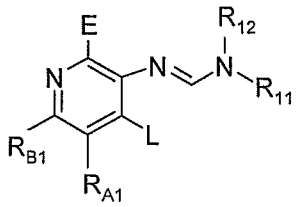
For certain embodiments, including any one of the above embodiments of methods (ix) through (xxiv), methods (ix-1) through (xxiv-1), methods (ix-2) through (xxiv-2),

methods (ix-3) through (xxiv-3), methods (ix-4) through (xxiv-4), methods (ix-5) through (xxiv-5), methods (ix-6) through (xxiv-6), methods (ix-7) through (xxiv-7), methods (ix-8) through (xxiv-8), methods (ix-9) through (xxiv-9), and methods (ix-10) through (xxiv-10), R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, wherein R_{A1}, R_{B1}, and R_{1a} are as defined above for embodiments wherein R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}. For the resulting embodiments of Formula I_a, I_a-2, I_a-3, I_a-4, I_a-5, I_a-6, and I_a-7, R_{2a} is hydrogen. For resulting embodiments of Formula X_a, XX_a, and XXI_a, R_{2a} is hydrogen.

For certain embodiments, including any one of the above embodiments of Formula XI, R_A is R_{A1}, R_B is R_{B1}, and R_1 is R_{1a}, wherein R_{A1}, R_{B1}, and R_{1a} are as defined above for embodiments wherein R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}.

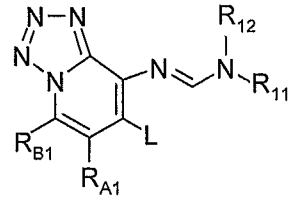
For each of the resulting embodiments, where present:

Formula VIII is Formula $VIII_a$:



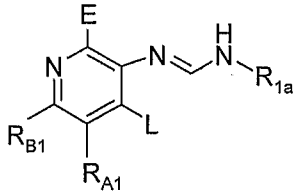
$VIII_a$;

Formula IX is Formula IX_a:



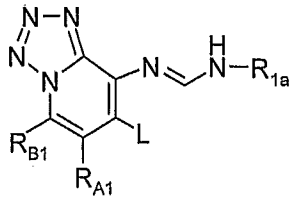
IX_a;

Formula XI is Formula XI_a:



XI_a;

and Formula XIII is Formula $XIII_a$:



$XIII_a$.

For each of the resulting embodiments, where present: R is R_a, R_3 is R_{3a}, R_4 is R_{4a}, R_5 is R_{5a}, and Y is Y_a.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, R_{1a} is selected from the group consisting of $-R_{4a}$, $-X-R_{4a}$, $-X-Y_a-R_{4a}$, $-X-Y_a-X-Y_a-R_{4a}$, $-X-R_{5a}$, $-N(R_1')-Q-R_{4a}$, $-N(R_1')-X_1-Y_1-R_{4a}$, and $-N(R_1')-X_1-R_{5b}$.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, R_{1a} is selected from the group consisting of $-R_{4a}$, $-X-R_{4a}$, $-X-Y_a-R_{4a}$, $-X-Y_a-X-Y_a-R_{4a}$, and $-X-R_{5a}$.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, R_{1a} is $-R_{4a}$ or $-X-R_{4a}$. For certain of these embodiments, $-R_{4a}$ is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, and (1-hydroxycyclobutyl)methyl, and $-X-R_{4a}$ is 2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl. For certain of these embodiments, R_{1a} is $-R_{4a}$, and $-R_{4a}$ is 2-methylpropyl or 2-hydroxy-2-methylpropyl. For certain of these embodiments, R_{1a} is $-R_{4a}$, and $-R_{4a}$ is 2-methylpropyl. Alternatively, for certain of these embodiments, R_{1a} is $-X-R_{4a}$, and $-X-R_{4a}$ is 2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, except for embodiments where R_{1a} is $-R_{4a}$ or $-X-R_{4a}$, R_{1a} is $-X-Y_a-R_{4a}$. For certain of these embodiments, X is C_{2-4} alkylene, and Y_a is $-S(O)_2-$ or $-N(R_8)-Q-$. For certain of these embodiments, $-X-Y_a-R_{4a}$ is selected from the group consisting of 2-(propylsulfonyl)ethyl, 2-methyl-2-

[(methylsulfonyl)amino]propyl, 4-methylsulfonylaminobutyl, and 2-(acetylamino)-2-methylpropyl.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, except for embodiments where R_{1a} is $-R_{4a}$, $-X-R_{4a}$, or $-X-Y_a-R_{4a}$, R_{1a} is $-X-R_{5a}$. For certain of these embodiments, $-X-R_{5a}$ is 4-[(morpholin-4-ylcarbonyl)amino]butyl.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, except for embodiments where R_{1a} is $-R_{4a}$, $-X-R_{4a}$, $-X-Y_a-R_{4a}$, $-X-Y_a-X-Y_a-R_{4a}$, or $-X-R_{5a}$, R_{1a} is selected from the group consisting of $-N(R_1')-Q-R_{4a}$, $-N(R_1')-X_1-Y_1-R_{4a}$, and $-N(R_1')-X_1-R_{5b}$.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, R_{2a} is selected from the group consisting of $-R_{4a}$, $-X-R_{4a}$, $-X-Y_a-R_{4a}$, and $-X-R_{5a}$.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, R_{2a} is $-R_{4a}$. For certain of these embodiments, R_{2a} is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, ethoxymethyl, and hydroxymethyl. For certain of these embodiments, R_{2a} is selected from the group consisting of hydrogen, methyl, ethyl, and ethoxymethyl.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$;

or R_{A1} and R_{B1} taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R_a group, or substituted by one R_{3a} group, or substituted by one R_a group and one R_{3a} group;

or R_{A1} and R_{B1} taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R_a groups.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain of these embodiments, R_{A1} and R_{B1} are each methyl.

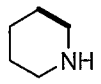
For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, and where R_{A1} and R_{B1} taken together can form a fused benzene ring, R_{A1} and R_{B1} taken together form a fused benzene ring wherein the benzene ring is unsubstituted or substituted by one R_a group, or substituted by one R_{3a} group, or substituted by one R_a group and one R_{3a} group. For certain of these embodiments, R_a is hydroxy or bromo, and R_{3a} is methoxy, phenoxy, or benzyloxy. For certain of these embodiments, the fused benzene ring is substituted by one R_a group selected from the group consisting of hydroxy and bromo. Alternatively, for certain of these embodiments, the fused benzene ring is substituted by one R_{3a} group wherein R_{3a} is methoxy, phenoxy, or benzyloxy. For certain embodiments, R_{A1} and R_{B1} taken together form a fused benzene ring that is unsubstituted.

For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, and where R_{A1} and R_{B1} taken together can form a fused pyridine ring, R_{A1} and R_{B1} taken together form a fused pyridine ring wherein the fused pyridine ring is unsubstituted or substituted by one R_a group, or substituted by one R_{3a} group, or substituted by one R_a group and one R_{3a} group; and wherein the fused pyridine ring is



, wherein the highlighted bond indicates the position where the ring is fused. For certain of these embodiments, R_a is hydroxy or bromo, and R_{3a} is methoxy, phenoxy, or benzyloxy. For certain of these embodiments, the fused pyridine ring is substituted by one R_a group selected from the group consisting of hydroxy and bromo. Alternatively, for certain of these embodiments, the fused pyridine ring is substituted by one R_{3a} group wherein R_{3a} is methoxy, phenoxy, or benzyloxy. Alternatively, for certain of these embodiments, the fused pyridine ring is unsubstituted.

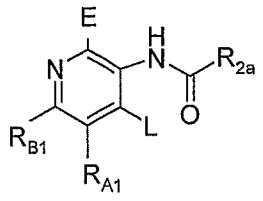
For certain embodiments, including any one of the above embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, embodiments where R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, and embodiments of XI_a, and where R_{A1} and R_{B1} taken together can form a fused 5 to 7 membered saturated ring, R_{A1} and R_{B1} taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R_a groups. For certain of these embodiments, R_{A1} and R_{B1} taken together form a fused 5 to 7 membered carbocyclic ring wherein the fused ring is unsubstituted or substituted by one or more R_a groups. For certain of these embodiments, the fused ring is a 6 membered carbocyclic ring which is unsubstituted. Alternatively, for certain of these embodiments, R_{A1} and R_{B1} taken together form a fused 5 to 7 membered saturated ring containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R_a groups. For certain of these embodiments, the fused ring is a fused 6 membered ring which is unsubstituted or substituted at a carbon atom by one or more R_a groups. For certain of these embodiments, the fused 6 membered ring is



wherein the ring is unsubstituted; and wherein the highlighted bond indicates the position where the ring is fused.

For certain embodiments, including any one of the above embodiments which includes a step of reacting the compound of Formula IV with an amine of the formula R_1NH_2, the step is carried out neat and at an elevated temperature.

For certain embodiments, including any one of the above embodiments wherein Formula IV is the Formula IV_a:

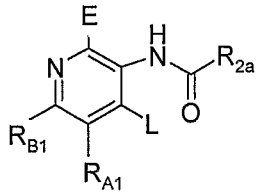


IV_a,

and which includes a step of reacting the compound of Formula IV_a with an amine of the formula $R_{1a}NH_2$, the step is carried out neat and at an elevated temperature.

For certain embodiments, including any one of the above embodiments which includes a step of reacting the compound of Formula IV with an amine of the formula R_1NH_2, the step is carried out in a solvent and at an elevated temperature, except for embodiments wherein the step is carried out neat. For certain of these embodiments, the solvent is selected from the group consisting of methanol, ethanol, trifluoroethanol, isopropanol, *tert*-butanol, water, acetonitrile, 1-methyl-2-pyrrolidinone, and toluene. For certain of these embodiments, the solvent is selected from the group consisting of trifluoroethanol, isopropanol, and *tert*-butanol.

For certain embodiments, including any one of the above embodiments wherein Formula IV is the Formula IV_a:



IV_a,

and which includes a step of reacting the compound of Formula IV_a with an amine of the formula $R_{1a}NH_2$, the step is carried out in a solvent and at an elevated temperature, except for embodiments wherein the step is carried out neat. For certain of these embodiments, the solvent is selected from the group consisting of methanol, ethanol, trifluoroethanol, isopropanol, *tert*-butanol, water, acetonitrile, 1-methyl-2-pyrrolidinone, and toluene. For certain of these embodiments, the solvent is selected from the group consisting of trifluoroethanol, isopropanol, and *tert*-butanol.

For certain embodiments, including any one of the above embodiments which includes a step of reacting the compound of Formula VIII with an amine of the formula R_1NH_2, the step is carried out neat. For certain of these embodiments, the amine is of the formula $R_{1a}NH_2$. For certain of these embodiments, the step is carried out at an elevated temperature. For certain of these embodiments, the compound of Formula VIII is of Formula $VIII_a$.

For certain embodiments, including any one of the above embodiments which includes a step of reacting the compound of Formula VIII with an amine of the formula R_1NH_2, the step is carried out in a solvent. For certain of these embodiments, the solvent is selected from the group consisting of methanol, ethanol, trifluoroethanol, isopropanol,

tert-butanol, water, acetonitrile, 1-methyl-2-pyrrolidinone, toluene, and tetrahydrofuran. For certain of these embodiments, the solvent is selected from the group consisting of trifluoroethanol, isopropanol, *tert*-butanol, and acetonitrile. For certain of these embodiments, the amine is of the formula $R_{1a}NH_2$. For certain of these embodiments, the step is carried out at an elevated temperature. For certain other of these embodiments, the step is carried out at room temperature. For certain of these embodiments, the compound of Formula VIII is of Formula $VIII_a$.

For certain embodiments, including any one of the above embodiments which includes an elevated temperature, the elevated temperature is not lower than 80 °C.

For certain embodiments, including any one of the above embodiments which includes an elevated temperature, the elevated temperature is not lower than 110 °C.

For certain embodiments, including any one of the above embodiments which includes an elevated temperature, the elevated temperature is not higher than 200 °C.

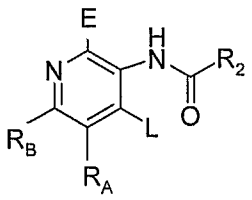
For certain embodiments, including any one of the above embodiments which includes an elevated temperature, the elevated temperature is not higher than 180 °C.

For certain embodiments, including any one of the above embodiments which includes an elevated temperature, the elevated temperature is not higher than 165 °C.

For certain embodiments, including any one of the above embodiments which includes an elevated temperature, the elevated temperature is not higher than 150 °C.

For certain embodiments, including any one of the above embodiments which includes an elevated temperature, the elevated temperature is not higher than 135 °C.

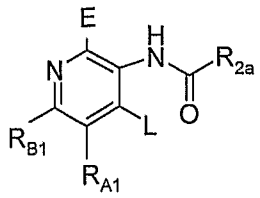
In one embodiment, the present invention provides a compound of the Formula IV:



IV

wherein R_A, R_B, R_2, E, and L are as defined above in method (i). For certain of these embodiments, R_A, R_B, R_2, E, and L are as defined in any one of the above embodiments of method (i).

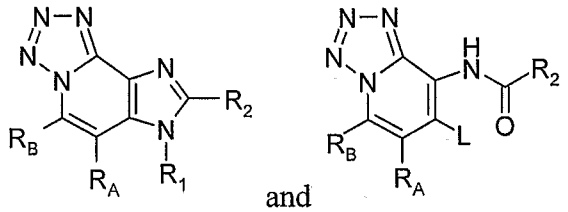
In another embodiment, the present invention provides a compound of the Formula IV_a:



IV_a,

wherein R_{A1}, R_{B1}, R_{2a}, E, and L are as defined above in method (i) where R_A is R_{A1}, R_B is R_{B1}, and R_2 is R_{2a}. For certain of these embodiments, R_{A1}, R_{B1}, R_{2a}, E, and L are as defined in any one of the above embodiments of method (i) where R_A is R_{A1}, R_B is R_{B1}, and R_2 is R_{2a}.

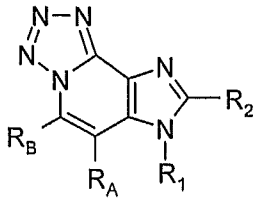
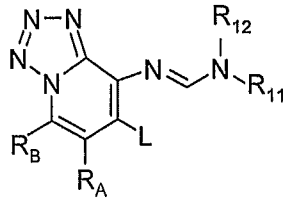
For certain embodiments, including any one of the above embodiments of method (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), or Formula IV or IV_a, E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or E is joined with the adjacent pyridine nitrogen atom to form the fused tetrazolo ring shown in Formulas I-1 and IV-1:



I-1 and IV-1.

For certain embodiments, including any one of the above embodiments of method (ix), (x), (xi), (xii), (xiii), (xiv), (xv), (xix), (xx), (xxi), or (xxii), E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formulas I and VIII to form the fused tetrazolo ring in Formulas I-1 and IX:

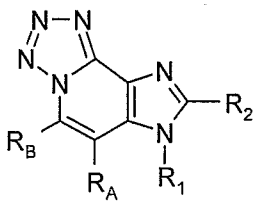
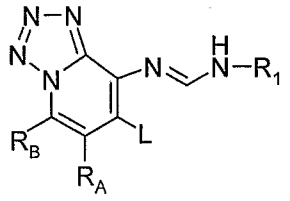



and

I-1 IX.

For certain embodiments, including any one of the above embodiments of method (xvi), (xvii), (xviii), (xxiii), and (xxiv) E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formulas I and XI to form the fused tetrazolo ring in Formulas I-1 and XIII:

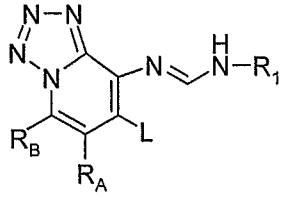



and

I-1 XIII.

For certain embodiments, including any one of the above embodiments of Formula XI or XI$_a$, E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formula XI to form the fused tetrazolo ring in Formula XIII:



XIII.

For certain of these embodiments, E is hydrogen. Alternatively, for certain of these embodiments, E is fluoro, chloro, bromo, or iodo, and for certain of these embodiments, E is chloro. Alternatively, for certain of these embodiments, E is hydroxy. Alternatively, for certain of these embodiments, E is phenoxy (OPh). Alternatively, for certain of these embodiments, E is -O-S(O)$_2$-R' wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro. Alternatively, for certain of these embodiments, E is -N(Bn)$_2$ wherein Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl. Alternatively, for certain of these embodiments, E is joined with the adjacent pyridine nitrogen atom to form the fused tetrazolo ring.

For certain embodiments, including any one of the above embodiments, L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro. For certain embodiments, including any one of the above embodiments, L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl or halo. For certain of these embodiments, L is fluoro, chloro, bromo, or iodo, and for certain of these embodiments, L is chloro. Alternatively, for certain of these embodiments, L is phenoxy. Alternatively, for certain of these embodiments, L is -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro. For certain of these embodiments, L is -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl or halo.

For certain embodiments, including any one of the above embodiments wherein R' is present, R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro. For certain embodiments, R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl or halo. For certain of these embodiments, R' is alkyl, and for certain of these embodiments, R' is methyl. Alternatively, for certain of these embodiments, R' is haloalkyl, and for certain of these embodiments, R' is trifluoromethyl. Alternatively, for certain of these embodiments, R' is aryl optionally substituted by alkyl or halo, and for certain of these embodiments, R' is phenyl, *p*-bromophenyl, or *p*-tolyl. For certain of these embodiments, R' is aryl optionally

substituted by alkyl, halo, or nitro, and for certain of these embodiments, R' is phenyl, *p*-bromophenyl, *p*-tolyl, 2-nitrophenyl, or 4-nitrophenyl.

For certain embodiments, including any one of the above embodiments wherein R is present, R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain of these embodiments, R is selected from the group consisting of hydroxy and bromo. For certain of these embodiments, R is at the 7- or 8- position. For certain of these embodiments, R is at the 7-position. Alternatively, for certain of these embodiments, R is at the 8-position.

For certain embodiments, including any one of the above embodiments wherein R is present except where R is selected from the group consisting of hydroxy and bromo, R is R_a.

For certain embodiments, including any one of the above embodiments wherein R_a is present, R_a is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, trifluoromethyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain of these embodiments, R_a is selected from the group consisting of hydroxy and bromo. For certain of these embodiments, R_a is at the 7- or 8- position. For certain of these embodiments, R_a is at the 7-position. Alternatively, for certain of these embodiments, R_a is at the 8-position.

For certain embodiments, including any one of the above embodiments wherein R_3 is present, R_3 is selected from the group consisting of $-Z-R_4$, $-Z-X-R_4$, $-Z-X-Y-R_4$, $-Z-X-Y-X-Y-R_4$, and $-Z-X-R_5$. For certain of these embodiments, R_3 is $-Z-R_4$ or $-Z-X-R_4$. For certain of these embodiments, R_3 is $-Z-R_4$. Alternatively, for certain of these embodiments, R_3 is $-Z-X-R_4$. For certain of any of these embodiments, Z is -O-. For certain of these embodiments, R_3 is methoxy, phenoxy, or benzyloxy. For certain of these embodiments, R_3 is at the 7- or 8-position. For certain of these embodiments, R_3 is at the 7-position. For certain of these embodiments, R_3 is a benzyloxy group at the 7-position. Alternatively, for certain of these embodiments, R_3 is at the 8-position.

For certain embodiments, including any one of the above embodiments wherein R_3 is present except where R_3 is $-Z-R_4$, $-Z-X-R_4$, methoxy, phenoxy, or benzyloxy, R_3 is R_{3a}.

For certain embodiments, including any one of the above embodiments wherein R_{3a} is present, R_{3a} is selected from the group consisting of $-Z-R_{4a}$, $-Z-X-R_{4a}$, $-Z-X-Y_a-R_{4a}$, $-Z-X-Y_a-X-Y_a-R_{4a}$, and $-Z-X-R_{5a}$. For certain of these embodiments, R_{3a} is $-Z-R_{4a}$ or

-Z-X-R_{4a}. For certain of these embodiments, R_{3a} is -Z-R_{4a}. Alternatively, for certain of these embodiments, R_{3a} is -Z-X-R_{4a}. For certain of any of these embodiments, Z is -O-. For certain of these embodiments, R_{3a} is methoxy, phenoxy, or benzyloxy. For certain of these embodiments, R_{3a} is at the 7- or 8-position. For certain of these embodiments, R_{3a} is at the 7-position. For certain of these embodiments, R_{3a} is a benzyloxy group at the 7-position. Alternatively, for certain of these embodiments, R_{3a} is at the 8-position.

For certain embodiments, including any one of the above embodiments wherein R_4 is present, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo. For certain of these embodiments, R_4 is alkyl optionally substituted by hydroxy or oxo. For certain of these embodiments, R_4 is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,2-dimethyl-4-oxopentyl, and (1-hydroxycyclobutyl)methyl. For certain of these embodiments, R_4 is 2-methylpropyl or 2-hydroxy-2-methylpropyl. For certain of these embodiments, R_4 is 2-methylpropyl.

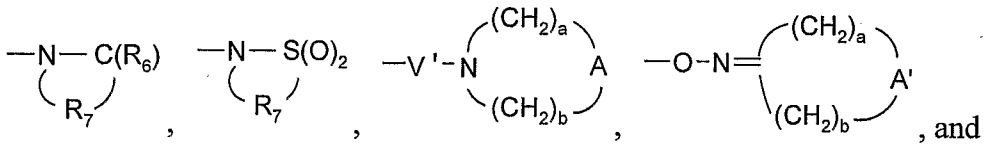
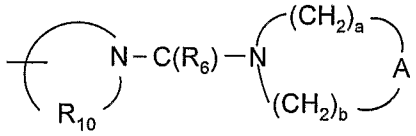
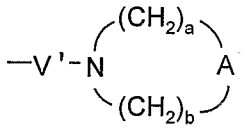
For certain embodiments, including any one of the above embodiments wherein R_4 is present in -X-Y-R_4, R_4 is C_{1-4} alkyl. For certain of these embodiments, R_4 is methyl.

For certain embodiments, including any one of the above embodiments wherein R_{4a} is present, R_{4a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl,

trifluoromethyl, trifluoromethoxy, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, and (dialkylamino)alkyleneoxy. For certain of these embodiments, R_{4a} is alkyl optionally substituted by hydroxy. For certain of these embodiments, R_{4a} is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, and (1-hydroxycyclobutyl)methyl. For certain of these embodiments, R_{4a} is 2-methylpropyl or 2-hydroxy-2-methylpropyl. For certain of these embodiments, R_{4a} is 2-methylpropyl.

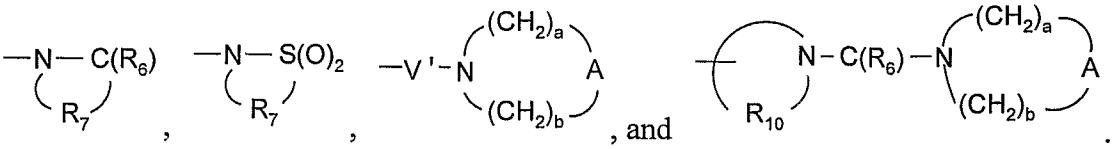
For certain embodiments, including any one of the above embodiments wherein R_{4a} is present in -X-Y-R_{4a}, R_{4a} is C_{1-4} alkyl. For certain of these embodiments, R_{4a} is methyl.

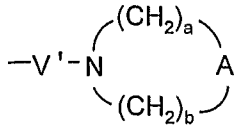
For certain embodiments, including any one of the above embodiments wherein R_5 is present, R_5 is selected from the group consisting of:


, and

. For certain of these embodiments, R_5 is

. For certain of these embodiments, V' is -NH-C(O)-. For certain of these embodiments, A is -O-. For certain of these embodiments, a and b are each 2.

For certain embodiments, including any one of the above embodiments wherein R_5 is present, R_5 is R_{5a}.

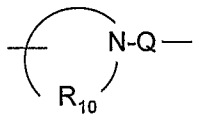
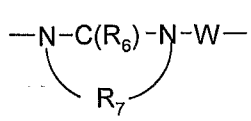
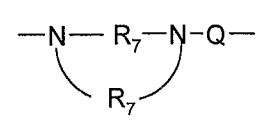
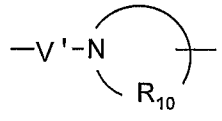
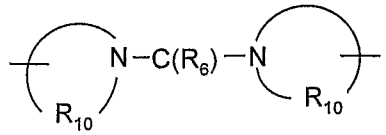
For certain embodiments, including any one of the above embodiments wherein R_{5a} is present, R_{5a} is selected from the group consisting of:


, and .

For certain of these embodiments, R_{5a} is . For certain of these embodiments, V' is -NH-C(O)-. For certain of these embodiments, A is -O-. For certain of these embodiments, a and b are each 2.

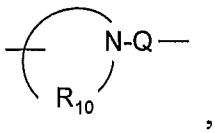
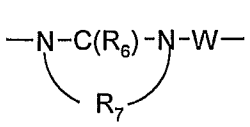
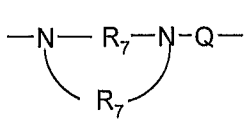
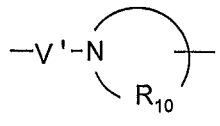
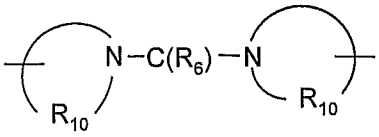
For certain embodiments, R_{11} and R_{12} are independently C_{1-4} alkyl or R_{11} and R_{12} together with the nitrogen atom to which they are attached form a 5- or 6-membered ring optionally containing -O-, –N(C_{1-4} alkyl)-, or -S-. For certain embodiments, R_{11} and R_{12} are each methyl.

For certain embodiments, including any one of the above embodiments where X is present, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups. For certain of these embodiments, X is C_{2-6} alkylene. For certain of these embodiments, X is C_{2-4} alkylene.

For certain embodiments, including any one of the above embodiments where Y is present, Y is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -C(R_6)-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-, -O-N(R_8)-Q-, , -O-N=C(R_4)-, -C(=N-O-R_8)-, -CH(-N(-O-R_8)-Q-R_4)-, , , , and . For certain of these embodiments, Y is -$S(O)_2$- or -N(R_8)-Q-.

For certain embodiments, including any one of the above embodiments where Y is present, Y is Y_a.

For certain embodiments, including any one of the above embodiments where Y_a is present, Y_a is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-,

-N(R_8)-Q-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-, , , , , and . For certain of these embodiments, Y_a is -S(O)$_2$- or -N(R_8)-Q-.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" refer to a divalent form of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are used when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes

a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene", "heteroarylene", and "heterocyclylene" refer to a divalent form of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene", and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

The term "fused 5 to 7 membered saturated ring" includes rings which are fully saturated except for the bond where the ring is fused.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, when more than one R' group is present, then each R' group is independently selected. In another example, in the formula $O(-C(O)-R_2)_2$, each R_2 group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

Preparation Of The Compounds

More specific details of the reactions described herein are discussed in the context of the following schemes.

Some embodiments of the invention are described below in Reaction Schemes I through IX. For more detailed description of the individual reaction steps, see the EXAMPLES section below. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents known to those skilled in the art can be substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the methods described below can be further elaborated in light of this disclosure using conventional methods well known to those skilled in the art.

In carrying out methods of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York, USA, 1999.

Conventional methods and techniques of separation and purification can be used to isolate compounds shown in the Reaction Schemes below. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

Methods of the invention are shown in Reaction Scheme I, wherein R_A, R_B, R_1, R_2, E, and L are as defined above. In step (1) or (1a) of Reaction Scheme I, a 3-nitropyridine, 3-nitroquinoline, or 3-nitronaphthyridine of Formula V or II is reduced to a 3-aminopyridine, 3-aminoquinoline, or 3-aminonaphthyridine of Formula VI or III, respectively. The reduction can be carried out by a number of conventional methods. For example, the reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon or Raney nickel. The hydrogenation can be conveniently carried out at room temperature in a Parr apparatus in a suitable solvent such as *N,N*-dimethylformamide (DMF). The reduction can also be carried out using nickel boride, prepared *in situ* from sodium borohydride and nickel(II) chloride. The nickel boride reduction is conveniently carried out by adding a solution of a compound of Formula V or II in a suitable solvent or solvent mixture such as

dichloromethane/methanol to a mixture of excess sodium borohydride and catalytic or stoichiometric nickel(II) chloride in methanol. The reaction can be carried out at room temperature. Alternatively the reduction can be carried out using a one- or two-phase sodium dithionite reduction. The sodium dithionite reduction can be conveniently carried out using the conditions described by Park, K. K.; Oh, C. H.; and Joung, W. K.; *Tetrahedron Lett.*, *34*, pp. 7445-7446 (1993) by adding sodium dithionite to a compound of Formula V or II in a mixture of dichloromethane and water at ambient temperature in the presence of potassium carbonate and ethyl viologen dibromide, ethyl viologen diiodide, or 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide.

Many compounds of Formula V and II are known; others can be prepared by known methods. For quinolines and [1,5]naphthyridines of Formula V and II in which E is hydrogen and L is chloro, see U. S. Patent Nos. 4,689,338 (Gerster) and 6,194,425 (Gerster et al.) and the references cited therein. Quinolines, tetrahydroquinolines, and pyridines of Formula II in which E and L are each chloro or -O-S(O)$_2$-R', can be prepared from compounds of Formula V in which E is hydroxy; see, for example, U. S. Patent Nos. 4,988,815 (André et al.), 5,395,937 (Nikolaides et al.), 5,352,784 (Nikolaides et al.), 5,446,153 (Lindstrom et al.), and 6,743,920 (Lindstrom et al.) and the references cited therein. For quinolines and naphthyridines of Formula V or II in which E is part of a tetrazolo ring and L is chloro or -O-S(O)$_2$-R', see U. S. Patent Nos. 6,194,425 (Gerster et al.) and 5,741,908 (Gerster et al.) and the references cited therein. Compounds of Formula II in which E and/or L is phenoxy can be prepared from compounds of Formula II in which E and/or L is chloro using the methods described in 6,743,920 (Lindstrom et al.). Compounds of Formula II in which E is -N(Bn)$_2$ can be prepared from compounds of Formula II in which E is -O-S(O)$_2$-R' according to the methods described in 5,395,937 (Nikolaides et al.) and 5,352,784 (Nikolaides et al.).

Several compounds of Formula VI in which E is hydrogen are known compounds, including unsubstituted and substituted pyridines, quinolines, and naphthyridines of each isomeric variation. See, for example, U.S. Patent No. 6,110,929 (Gerster et al.) and the references cited therein. Also, some compounds of Formula III are known. For example, 3-amino-4-chloroquinoline, 3-amino-4,5-dichloroquinoline, and 3-amino-4,7-dichloroquinoline have been prepared by Surrey et al., *Journal of the American Chemical Society*, 73, pp. 2413-2416 (1951).

In step (2) or (3a) of Reaction Scheme I, a 3-aminopyridine, 3-aminoquinoline, or 3-aminonaphthyridine of Formula VI or III is reacted with a carboxylic acid or an equivalent thereof to provide an amide-substituted compound of Formula VII or IV, respectively. Suitable equivalents to carboxylic acids include acid anhydrides and acid halides. The selection of the carboxylic acid equivalent is determined by the desired substituent at R_2. For example, the use of butyryl chloride provides a compound in which R_2 is a propyl group; the use of ethoxyacetyl chloride provides a compound in which R_2 is an ethoxymethyl group. The reaction can be conveniently carried out by combining an acid halide of Formula $R_2C(O)Cl$ or $R_2C(O)Br$ with a compound of Formula VI or III in a suitable solvent such as dichloromethane, acetonitrile, or 1,2-dichloroethane optionally in the presence of a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine (DMAP). The reaction can be run at a reduced temperature, for example, 0 °C, at room temperature, or at an elevated temperature, such as 40 °C to 90 °C. For compounds wherein R_2 is hydrogen, a compound of Formula VI or III can be reacted with a formylating agent such as, for example, diethoxymethyl acetate or acetic formic anhydride. Some compounds of Formula VII are known; see, for example, U.S. Patent No. 6,110,929 (Gerster et al.).

In step (3) of Reaction Scheme I, the hydroxy group in a compound of Formula VII is converted to a leaving group using conventional activation methods to provide a compound of Formula IV. For example, conversion of the hydroxy group to a chloro group can be conveniently carried out by combining a compound of Formula VII with phosphorus(III) oxychloride. The chlorination reaction can be carried out neat or in a suitable solvent such as *N*,*N*-dimethylformamide (DMF), dichloromethane, acetonitrile, 1-methyl-2-pyrrolidinone (NMP), and 1,2-dichloroethane. The reaction can be carried out at room temperature or at an elevated temperature up to the reflux temperature, for example, at a temperature of 25 °C to 120 °C. Other examples of chlorinating agents include, for example, thionyl chloride, phosgene, oxalyl chloride, and phosphorus pentachloride. Other halogenating agents include phosphorus(III) oxybromide, phosphorus pentabromide, diphenylphosphinic chloride, and triphenylphosphine in the presence of bromine. The hydroxy group in a compound of Formula VII can also be converted to a sulfonate ester by reaction with, for example, a sulfonyl halide or sulfonic anhydride. Suitable sulfonating agents include methanesulfonyl chloride, methanesulfonic anhydride,

trifluoromethanesulfonyl chloride, trifluoromethanesulfonic anhydride, *N*-phenylbis(trifluoromethanesulfonimide), benzenesulfonyl chloride, benzenesulfonic anhydride, *p*-bromobenzenesulfonyl chloride, *p*-bromobenzenesulfonic anhydride, *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride, 2-nitrobenenesulfonyl chloride and 4-nitrobenzenesulfonyl chloride. The reaction with a sulfonating agent is typically carried out in the presence of a base. Preferably the base is a tertiary amine such as triethylamine. The reaction can be carried out in a suitable solvent such as dichloromethane, 1,2-dichloroethane, acetonitrile, tetrahydrofuran (THF), DMF, and NMP. The reaction may also be carried out in pyridine, which can be used as both the base and the solvent for the reaction. The reaction may be carried out at room temperature or an elevated temperature, such as the reflux temperature of the solvent. Preferably the reaction temperature is about room temperature to no higher than 90 °C. These methods described for step (3) of Reaction Scheme I can also be used to convert a 3-aminopyridine, 3-aminoquinoline, or 3-aminonaphthyridine of Formula VI to a compound of Formula III, as shown in step (2a) of Reaction Scheme I.

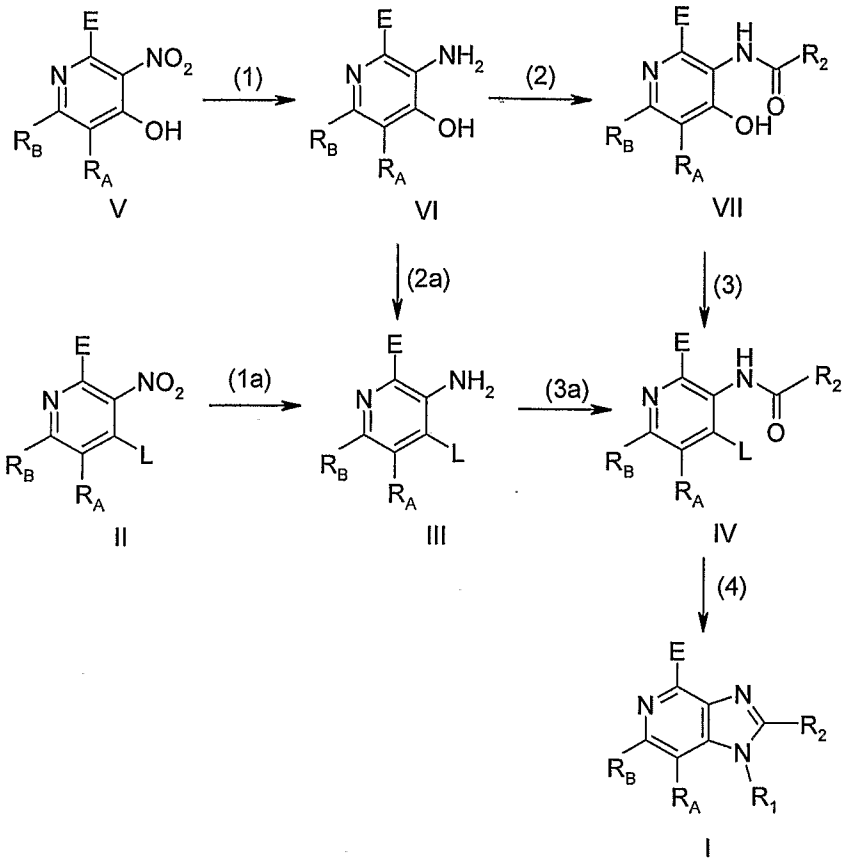
In step (4) of Reaction Scheme I, an amide of Formula IV is reacted with an amine of formula R_1NH_2, or a suitable salt thereof, to provide a 1*H*-imidazo compound of Formula I. The reaction may be carried out neat at an elevated temperature such as the temperature required to melt the mixture. The reaction may also be carried out in a suitable solvent at an elevated temperature. Suitable solvents include alcohols such as methanol, ethanol, trifluoroethanol, isopropanol, and *tert*-butanol; water; acetonitrile; NMP; and toluene. Preferred solvents include trifluoroethanol, isopropanol, and *tert*-butanol. Preferably, the reaction temperature is not lower than 80 °C and not higher than 200 °C. More preferably, the reaction temperature is not higher than 180 °C. More preferably, the reaction temperature is 110 °C to 165 °C. Optionally, a base may be used in the reaction. Suitable bases include triethylamine. Optionally, a catalyst such as pyridine hydrochloride, pyridinium *p*-toluenesulfonate, or *p*-toluenesulfonic acid can be added. For some amines of formula R_1NH_2 under certain conditions, an uncyclized 3-amido-4-amino intermediate may be isolated. The intermediate can then be cyclized in a subsequent step by heating in a solvent such as toluene, optionally in the presence of a catalyst such as pyridine hydrochloride or pyridinium *p*-toluenesulfonate. The cyclization

may be carried out at an elevated temperature, such as the reflux temperature of the solvent.

Numerous primary amines of formula R_1NH_2, or salts thereof, suitable for this reaction are commercially available; others can be prepared by known methods. See, for example, the methods in U.S. Patent Nos. 6,451,810 (Coleman et al.), 6,660,747 (Crooks et al.), 6,683,088 (Crooks et al.), and 6,656,938 (Crooks et al.); U. S. Patent Application Publication No. 2004/0147543 (Hays et al.); and International Publication No. WO2005/051317 (Krepski et al.).

Some amines of the formula R_1NH_2 can be made according to the following method. For some embodiments, R_1 is a 1-hydroxycycloalkylmethyl group. The corresponding amine of formula R_1NH_2 can be prepared by combining a cyclic ketone, such as cyclopentanone or cyclobutanone with excess nitromethane in a suitable solvent such as ethanol or methanol in the presence of a catalytic amount of base such as sodium ethoxide or sodium hydroxide and reducing the resultant nitromethyl-substituted compound using conventional heterogeneous hydrogenation conditions. The hydrogenation is typically carried out in the presence of a catalyst such as palladium hydroxide on carbon, palladium on carbon, or Raney nickel in a suitable solvent such as ethanol. Both the reaction with nitromethane and the reduction can be carried out at room temperature. A wide variety of cyclic ketones can be obtained from commercial sources; others can be synthesized using known synthetic methods.

Reaction Scheme I



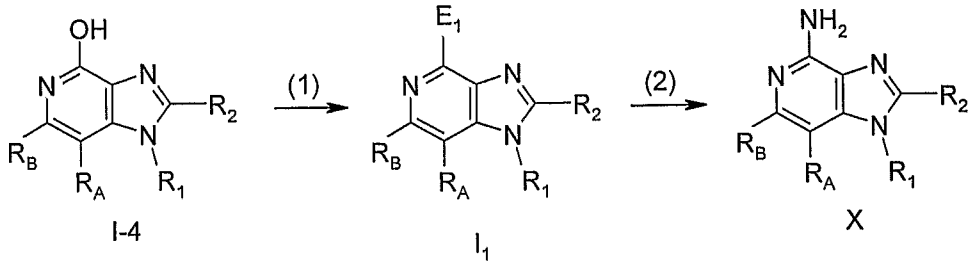
I

A compound of Formula I can be converted to a compound of Formula X using a variety of methods, depending on the identity of E. Examples of these methods are shown in Reaction Schemes II through V.

For certain embodiments, the amination of a compound of Formula I_1 is shown in Reaction Scheme II, wherein E_1 is a halogen, phenoxy, or -O-S(O)$_2$-R', and R_A, R_B, R_1, R_2 are as defined above. Step (1) of Reaction Scheme II can be used to convert a compound of Formula I-4, wherein E is hydroxy, to a compound of Formula I_1. Any one of the methods described in step (3) and step (2a) of Reaction Scheme I can be used. The amination in step (2) of Reaction Scheme II can be conveniently carried out by heating a combination of a compound of Formula I_1 and a solution of ammonia in a suitable solvent such as methanol. The amination may also be carried out by using ammonium acetate or ammonium hydroxide in combination with a compound of Formula I_1 and heating. The amination is preferably carried out at a temperature not lower than 100 °C, preferably not lower than 125 °C, more preferably not lower than 140 °C. The reaction is preferably

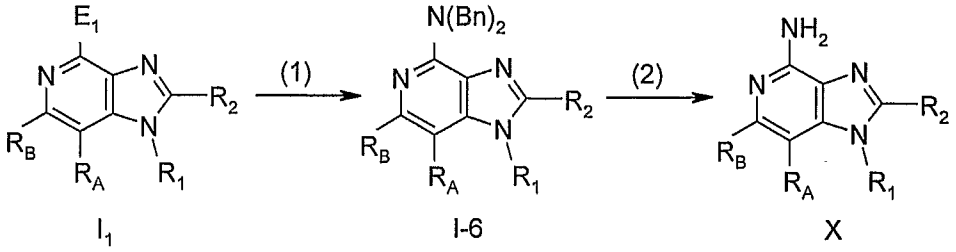
carried out at a temperature not higher than 200 °C, more preferably not higher than 170 °C.

Reaction Scheme II



Alternatively, a compound of Formula I_1 can be converted in two steps to a compound of Formula X as shown in Reaction Scheme III, wherein R_A, R_B, R_1, R_2, E_1, and Bn are as defined above. Step (1) of Reaction Scheme III can be used to displace the E_1 group in a compound of Formula I_1 with an amine of Formula $HN(Bn)_2$ to provide a compound of Formula I-6. The displacement can be conveniently carried out by combining an amine of formula $HN(Bn)_2$ and a compound of Formula I_1 in a suitable solvent such as toluene or xylenes in the presence of a base such as triethylamine and heating at an elevated temperature such as the reflux temperature of the solvent. In step (2) of Reaction Scheme III, the protecting groups are removed from the 4-amine of a compound of Formula I-6 to provide a compound of Formula X. For certain embodiments, the deprotection can be conveniently carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol. Alternatively, when Bn is *p*-methoxybenzyl, step (2) may carried out by combining trifluoroacetic acid and a compound of Formula I-6 and stirring at room temperature or heating at an elevated temperature such as 50 °C to 70 °C.

Reaction Scheme III

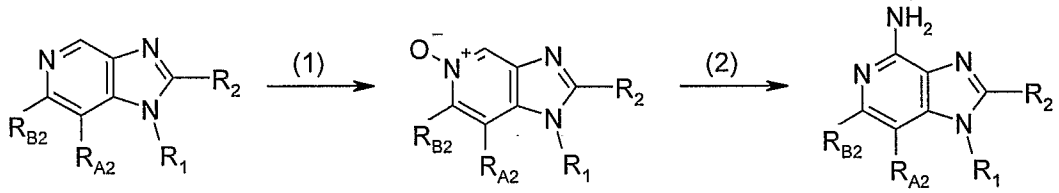


For certain embodiments, a compound of Formula I wherein E is hydrogen can be converted in to a compound of Formula X_2 by oxidation and amination as shown in Reaction Scheme IV, wherein R_{A2} and R_{B2} taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group, and R_1 and R_2 are as defined above. In step (1) of Reaction Scheme IV, a compound of Formula I-2_2 is oxidized to a 5*N*-oxide of Formula XX_2 using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by combining 3-chloroperoxybenzoic acid with a compound of Formula I-2_2 in a suitable solvent such as dichloromethane or chloroform. The reaction can be carried out at room temperature. Alternatively, other peracids such as peracetic acid can be used as the oxidizing agent. The reaction with peracetic acid can be carried out in a suitable solvent such as ethanol at an elevated temperature such as 50 °C to 60 °C. The 5*N*-oxide of Formula XX_2 is then aminated in step (2) of Reaction Scheme IV to provide a compound of Formula X_2. The amination can be carried out by the activation of the 5*N*-oxide by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding *p*-toluenesulfonyl chloride to a mixture of ammonium hydroxide and a solution of the 5*N*-oxide in a suitable solvent such as dichloromethane or chloroform. The reaction can be carried out at room temperature. The oxidation and amination steps may be carried out as a one-pot procedure

without isolating the 5*N*-oxide of Formula XX_2. Alternatively, the 5*N*-oxide can be treated in step (2) with an isocyanate wherein the isocyanato group is bonded to a hydrolytically active functional group; subsequent hydrolysis of the resulting intermediate provides a compound of Formula X_2. The reaction can be conveniently carried out in two steps by (i) combining an isocyanate such as trichloroacetyl isocyanate and a solution of the 5*N*-oxide in a solvent such as dichloromethane and stirring at room temperature to provide an isolable amide intermediate. In step (ii), a solution of the intermediate in methanol can be treated with a base such as sodium methoxide at room temperature.

Alternatively, a 5*N*-oxide of Formula XX can be converted to a compound of Formula I_1 wherein E_1 is chloro using one of the methods described in step (3) of Reaction Scheme I. The resulting 4-chloro compound can then be aminated according to the methods described in Reaction Scheme II.

Reaction Scheme IV

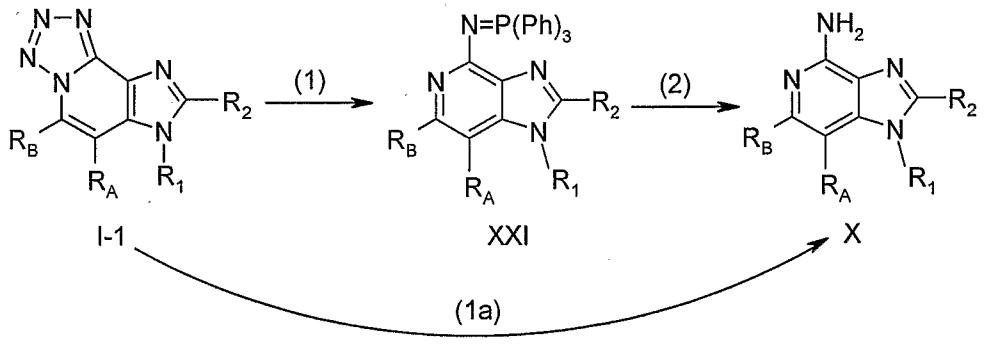


For embodiments wherein E is joined with the pyridine nitrogen atom in a compound of Formula I to form a fused tetrazolo ring, the tetrazolo ring can be removed to form a compound of Formula X as shown in Reaction Scheme V, wherein R_A, R_B, R_1, and R_2 are as defined above, and Ph is phenyl. In step (1) of Reaction Scheme V, a compound of Formula I-1 is combined with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate of Formula XXI. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature.

In step (2) of Reaction Scheme V, an *N*-triphenylphosphinyl intermediate of Formula XXI is hydrolyzed to provide a compound of Formula X. The hydrolysis can be carried out by general methods well known to those skilled in the art, for example, by

heating in a lower alkanol or an alkanol/water solution in the presence of an acid such as trifluoroacetic acid, acetic acid, or hydrochloric acid. A compound of Formula X may also be obtained through an alternative route as shown in step (1a) of Reaction Scheme V. In step (1a), the tetrazolo ring is reductively removed from a compound of Formula I-1 to provide a compound of Formula X. The reaction can be carried out by reacting the compound of Formula I-1 with hydrogen in the presence of a catalyst and an acid. The hydrogenation can be conveniently run at ambient temperature on a Parr apparatus with a suitable catalyst, such as platinum IV oxide, and a suitable acid, such as trifluoroacetic acid or hydrochloric acid. The reaction can optionally be carried out in the presence of a solvent such as, for example, ethanol. If step (1a) is used, a compound of Formula I-1 in which R_A and R_B taken together form a fused benzene ring or a fused pyridine ring may be converted to a compound of Formula X in which R_A and R_B taken together form a fused 5 to 7-membered saturated ring optionally containing one nitrogen atom. One of skill in the art would understand that other groups susceptible to reduction, such as alkenyl, alkynyl, and aryl groups, would be reduced in step (1a).

Reaction Scheme V

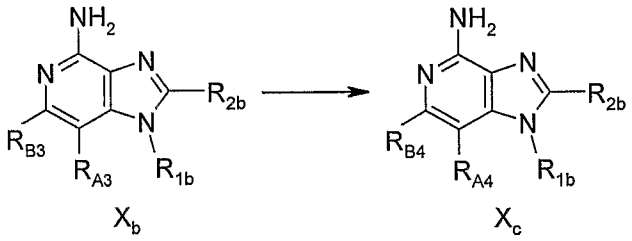


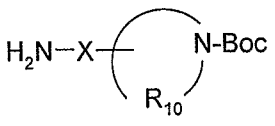
For certain embodiments, compounds of Formula X_b can be reduced according to Reaction Scheme VI, wherein R_{A3} and R_{B3} taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R_b group, or substituted by one R_{3b} group, or substituted by one R_b group and one R_{3b} group; R_{A4} and R_{B4} taken together form a fused 5 to 7-membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R_b groups; and R_{1b}, R_{2b}, R_{3b}, and R_b are subsets of R_1, R_2, R_3, and R as defined above that do not include those substituents that

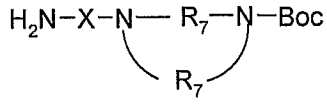
one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

As shown in Reaction Scheme VI, an 1*H*-imidazo[4,5-*c*]quinolin-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula X_b can be reduced to a 6,7,8,9-tetrahydroquinoline or tetrahydronaphthyridine of Formula X_c. Compounds of Formula X_b can be prepared according to the methods described in Reaction Schemes II, III, IV, or V. The reaction is conveniently carried out under hetereogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula X_b in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature.

Reaction Scheme VI

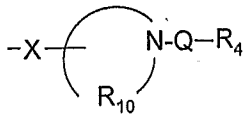
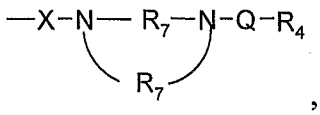


For some embodiments, compounds shown in Reaction Schemes I through VI can be further elaborated using conventional synthetic methods. Amines of formula R_1NH_2, used in step (4) of Reaction Scheme I, may contain a protected functional group, such as a *tert*-butoxycarbonyl-protected amino group. For example, protected diamines of Formula Boc-N(R_8)-X-NH_2, 

, or 

are commercially available or can be prepared by known methods; see, for example, U.S. Patent Nos. 6,660,747 (Crooks et al.), 6,683,088 (Crooks et al.), and 6,656,938 (Crooks et al.) and Carceller, E. et al., *J. Med. Chem., 39*, pp.487-493 (1996). The protecting group may be removed after the cyclization step shown in step (4) of Reaction Scheme I or after the steps shown in Reaction Schemes II through VI to reveal, for example, an amino substituent on the R_1 group. An amino group introduced in this manner can react with an acid chloride of Formula $R_4C(O)Cl$, a sulfonyl chloride of Formula $R_4S(O)_2Cl$, a sulfonic

anhydride of Formula $(R_4S(O)_2)_2O$, or an isocyanate of Formula $R_4N=C=O$ to provide a compound of Formula X in which R_1 is

–X-N(R_8)-Q-R_4, , or , where X, R_4, R_7, R_8, and R_{10} are as defined above and Q is -C(O)-, -SO_2-, or -C(O)-NH-. Numerous acid chlorides, sulfonyl chlorides, sulfonic anhydrides, and isocyanates are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by combining the acid chloride, sulfonyl chloride, sulfonic anhydride, or isocyanate and a solution of an amino-substituted compound, and a base such as triethylamine in a suitable solvent such as dichloromethane. The reaction can be carried out at room temperature.

Amines of formula R_1NH_2 can also contain other protected functional groups, such as ketal-protected ketones. For example, 2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)propylamine, prepared in Example 22 of International Publication No. WO2005/051317 (Krepski et al.), can be used in step (4) of Reaction Scheme I. The ketal protecting group can later be removed by conventional methods to provide a compound of Formula I or X in which R_1 is 2,2-dimethyl-4-oxopentyl.

Amino alcohols of formula H_2N-X-OH can be used in step (4) of Reaction Scheme I, and the hydroxy functional group can be converted in subsequent steps to a compound of Formula I or X having an –X-$S(O)_{0-2}$-R_4, –X-$S(O)_2$-N(R_8)-R_4, –X-O-N(R_8)-Q-R_4, –X-O-N=C(R_4)-R_4, –X-CH(-N(-O-R_8)-Q-R_4)-R_4 group at the R_1 position using methods described in U. S. Patent No. 6,664,264 (Dellaria et al.) and International Publication Nos. WO2005/066169 (Bonk and Dellaria), WO2005/018551 (Kshirsagar et al.), WO2005/018556 (Kshirsagar et al.), and WO2005/051324 (Krepski et al.), respectively.

The amine used in step (1) may be *tert*-butyl carbazate, and the resulting compound of Formula I or subsequently converted compound of Formula X wherein R_1 is a Boc-protected amino group can be deprotected to provide a 1-amino compound or a salt (for example, hydrochloride salt) thereof. The deprotection can be carried out by heating at reflux a solution of a compound of Formula I or X in ethanolic hydrogen chloride. The resulting compound of Formula I or X wherein R_1 is an amino group can treated with a ketone, aldehyde, or corresponding ketal or acetal thereof, under acidic conditions. For example, a ketone can be added to a solution of the hydrochloride salt of a compound of

Formula I or X in which R_1 is an amino group in a suitable solvent such as isopropanol or acetonitrile in the presence of an acid such as pyridinium *p*-toluene sulfonate or acetic acid, or an acid resin, for example, DOWEX W50-X1 acid resin. The reaction can be performed at an elevated temperature. The resulting imine can be reduced to provide a compound of Formula I or X in which R_1 is $-N(R_1')-Q-R_4$, wherein Q is a bond The reduction can be carried out at room temperature with sodium borohydride in a suitable solvent, for example, methanol. A *tert*-butyl hydrazinecarboxylate can also be manipulated in subsequent steps using the methods of U.S. Patent Application Publication No. 2005/0054640 to provide other compounds of Formula I or X, wherein R_1 is $-N(R_1')-Q-R_4$, $-N(R_1')-X_1-Y_1-R_4$, or $-N(R_1')-X_1-R_{5b}$.

Other transformations at the R_1 position can be made. See, for example, U.S. Patent Nos. 5,389,640 (Gerster et al.), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.), 6,660,747 (Crooks et al.), 6,670,372 (Charles et al.), 6,683,088 (Crooks et al.), 6,656,938 (Crooks et al.), 6,664,264 (Dellaria et al.), 6,677,349 (Griesgraber), and 6,664,260 (Charles et al.).

For some embodiments, synthetic transformations can be made at the R_2 position in a compound of Formula I or X, if, for example, the carboxylic equivalent used in step (2) or (3a) of Reaction Scheme I contains a protected or unprotected hydroxy group or a protected amino group. Some carboxylic acid equivalents of this type are commercially available; others can be prepared by known synthetic methods. A protected hydroxy or amino group installed at the R_2 position can be deprotected by a variety of methods well known to one of skill in the art. For example, a hydroxyalkylenyl group is conveniently introduced at the R_2 position by the dealkylation of a methoxy- or ethoxyalkylenyl group, which can be installed by using a methoxy- or ethoxy-substituted carboxylic acid equivalent in step (2) or (3a) of Reaction Scheme I. The dealkylation can be carried out by treating a compound of Formula I or Formula X wherein R_2 is an alkoxyalkylenyl group with boron tribromide in a suitable solvent such as dichloromethane at a sub-ambient temperature such as 0 °C. The resulting hydroxy group may then be oxidized to an aldehyde or carboxylic acid or converted to a leaving group such as, for example, a chloro group using thionyl chloride or a trifluoromethanesulfonate group using trifluoromethanesulfonic anhydride. The resulting leaving group can then be displaced by a variety of nucleophiles. Sodium azide can be used as the nucleophile to install an azide

group, which can then be reduced to an amino group using heterogeneous hydrogenation conditions. An amino group at the R_2 position can be converted to an amide, sulfonamide, sulfamide, or urea using conventional methods. A leaving group at R_2, such as a chloro or trifluoromethanesulfonate group, can also be displaced with a secondary amine, a substituted phenol, or a mercaptan in the presence of a base such as potassium carbonate. For examples of these and other methods used to install a variety of groups at the R_2 position, see U.S. Patent No. 5,389,640 (Gerster et al.). These synthetic transformations may conveniently be carried out as the last steps in the synthesis or prior to the steps shown in Reaction Schemes II through VI.

1*H*-Imidazo[4,5-*c*]quinolines of Formulas II and V wherein the quinoline ring is substituted by a bromo, a benzyloxy, or a methoxy substituent and E is hydrogen are known or can be made according to the methods described in U. S. Patent Application Publication No. 2004/0147543 (Hays et al.) and International Publication No. WO2005/020999 (Lindstrom et al.). These compounds can be subjected to the methods of Reaction Scheme I to provide 1*H*-imidazo[4,5-*c*]quinolines of Formula I-2_2, which can then be oxidized and aminated according to the methods of Reaction Scheme IV. Compounds in which the quinoline ring is substituted by a benzyloxy or methoxy group can then be converted to a hydroxy-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXII, shown below in Reaction Scheme VII. The demethylation of a methoxy-substituted compound can be carried out with boron tribromide as described in the previous paragraph. Alternatively, the demethylation can be carried out by heating the methoxy-substituted compound with anhydrous pyridinium chloride at an elevated temperature, such as 210 °C. Removal of a benzyloxy group can be carried out as described in International Publication No. WO2005/020999 (Lindstrom et al.).

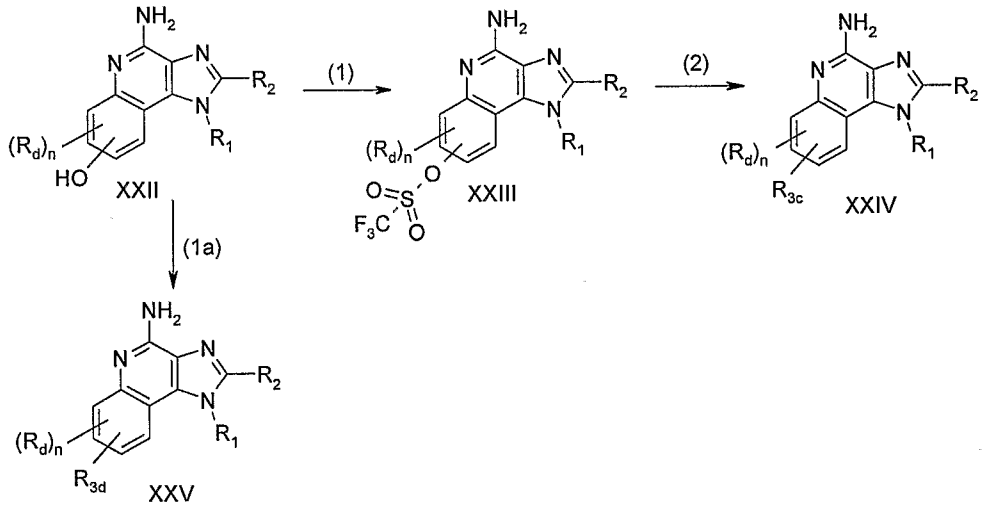
Further synthetic elaboration of 1*H*-imidazo[4,5-*c*]quinolin-4-amines can then be carried out as shown in Reaction Scheme VII, wherein R_{3c} is $-R_4$, $-X-R_4$, $-X-Y-R_4$, $-X-Y-X-Y-R_4$, or $-X-R_5$; R_{3d} is $-O-R_4$, $-O-X-R_4$, $-O-X-Y-R_4$, $-O-X-Y-X-Y-R_4$, or $-O-X-R_5$; R_d is selected from the group consisting of halogen, alkyl, alkenyl, trifluoromethyl, and dialkylamino; n is 0 or 1; and R_1 and R_2 are defined as above. In step (1) of Reaction Scheme VII, the hydroxy group of a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXII is activated by conversion to a trifluromethanesulfonate (triflate) group according to any

one of the methods described in step (2a) or (3) of Reaction Scheme I to provide a compound of Formula XXIII.

Step (2) of Reaction Scheme VII can be carried out using known palladium-catalyzed coupling reactions such as the Suzuki coupling, Heck reaction, the Stille coupling, and the Sonogashira coupling according to any of the methods described in U. S. Patent Application Publication No. 2004/0147543 (Hays et al.) to provide a compound of Formula XXIV. Compounds in which a bromo substituent is used instead of a triflate group in a compound of Formula XXIII can alternatively be used in this transformation. The Suzuki coupling is carried out with an aryl or vinyl boronic acid, an anhydride thereof, or a boronic acid ester. The Heck reaction is carried out with vinyl-substituted compound. Sonogashira and Stille coupling reactions can be carried out with alkynes, and any of the unsaturated compounds prepared by theses couplings can undergo reduction of an alkenylene or alkynylene group.

In step (1a) of Reaction Scheme VII, a hydroxy-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXII is converted to a compound of Formula XXV using a Williamson-type ether synthesis. The methods described in International Publication Nos. WO2005/020999 (Lindstrom et al.) and WO2005/032484 (Lindstrom et al.) can be used.

Reaction Scheme VII



For certain embodiments, methods of the invention are shown Reaction Scheme VIII, wherein R_A, R_B, R_1, R_{11}, R_{12}, E, and L are as defined above. In step (1) of Reaction Scheme VIII, a 3-aminopyridine, 3-aminoquinoline, or 3-aminonaphthyridine of Formula

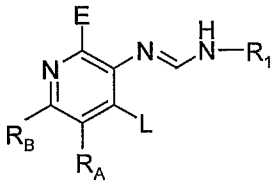
VI is converted to an imidoformamide of Formula VIII. The reaction can be carried out by combining a 3-aminopyridine, 3-aminoquinoline, or 3-aminonaphthyridine of Formula VI or a suitable salt thereof with a halogenating agent or sulfonating agent described in step (3) or (2a) of Reaction Scheme I in the presence of a formamide of formula $HC(O)\text{-}N(R_{11})R_{12}$. Several formamides of formula $HC(O)\text{-}N(R_{11})R_{12}$ are commercially available, such as, for example, DMF, *N,N*-diethylformamide, and 1-formylpiperidine. Other formamides of this formula can be prepared by known methods; for example, an amine can be combined with a mixture of formic acid and acetic anhydride in a suitable solvent such as THF, acetone, acetonitrile, ethyl acetate, *tert*-butyl methyl ether, DMF, NMP, dichloromethane, toluene, xylenes, methanol, and ethanol. The reaction can be carried out at room temperature, below room temperature at a temperature of about 0 °C up to room temperature, or at an elevated temperature up to the reflux temperature of the solvent. Step (1) of Reaction Scheme VIII may be carried out in a solvent such as dichloromethane, 1,2-dichloroethane, acetonitrile, THF, toluene, and NMP, or in some embodiments, the reaction can be carried out in excess DMF. The reaction may be carried out at room temperature, below room temperature such as a temperature not lower than 0 °C, or at an elevated temperature, such as a temperature not higher than the reflux temperature of the solvent. For some embodiments, the reaction temperature is not higher than 40 °C. For some embodiments, step (1) of Reaction Scheme VIII can be carried out by combining a compound of Formula VI with phosphorus(III) oxychloride in excess DMF at room temperature or at an elevated temperature such as a temperature not higher than 150 °C. For some embodiments, DMF may be used as the solvent. For some embodiments, the reaction temperature is 15 °C to 30 °C.

For some embodiments, the conversion of a 3-aminopyridine, 3-aminoquinoline, or 3-aminonaphthyridine of Formula VI to a imidoformamide of Formula VIII can be carried out in two steps, such as steps (1a) and (2a) or (1b) and (2b) of Reaction Scheme VIII. Steps (1b) and (2a) can be carried out according to the methods described in step (3) or (2a) of Reaction Scheme I in a solvent other than DMF. Steps (1a) and (2b) can be carried out as described in step (1) of Reaction Scheme VIII but in the absence of a halogenating or sulfonating agent.

In step (3) of Reaction Scheme VIII, an imidoformamide of Formula VIII is reacted with an amine of formula R_1NH_2, or a suitable salt thereof, to provide a 1*H*-

imidazo compound of Formula I-H. The reaction may be carried out neat at an elevated temperature such as the temperature required to melt the mixture. The reaction may also be carried out in a suitable solvent at room temperature or at an elevated temperature. Suitable solvents include alcohols such as methanol, ethanol, trifluoroethanol, isopropanol, and *tert*-butanol; water; acetonitrile; NMP; toluene, and tetrahydrofuran. Preferred solvents include trifluoroethanol, isopropanol, *tert*-butanol, and acetonitrile. Preferably, the reaction temperature is not higher than 250 °C. The reaction may be carried out at a temperature not higher than 200 °C or at a temperature not higher than 180 °C. Optionally, a base may be used in the reaction. Suitable bases include triethylamine. Optionally, a catalyst such as pyridine hydrochloride, pyridinium *p*-toluenesulfonate, or *p*-toluenesulfonic acid can be added.

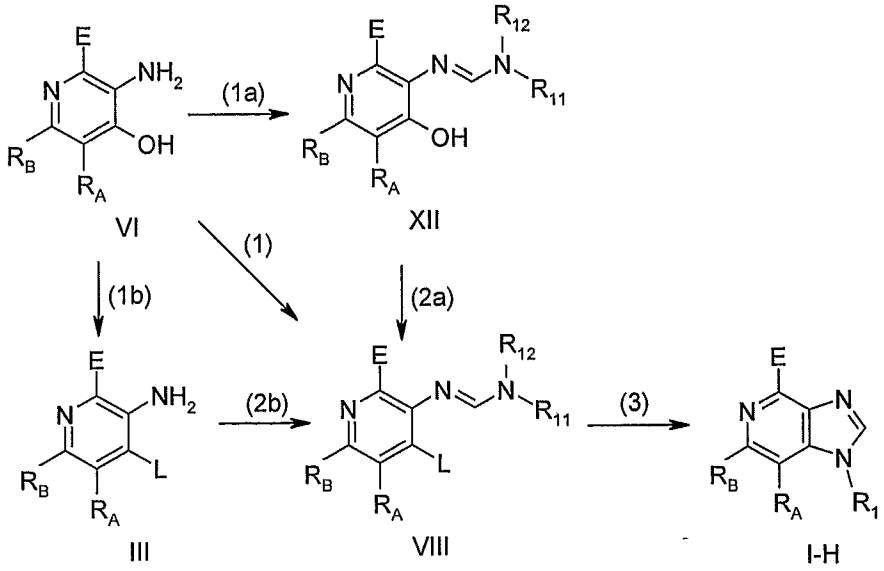
Under certain conditions, an imidoformamide intermediate of Formula XI,



XI , may be formed during step (3) of Reaction Scheme VIII. For some embodiments, the intermediate of Formula XI is isolated from the reaction mixture. The intermediate can then be cyclized in a subsequent step. The cyclization may be carried out by heating optionally in a solvent such as those described in the previous paragraph and optionally in the presence of a catalyst such as pyridine hydrochloride, pyridinium *p*-toluenesulfonate, or *p*-toluenesulfonic acid. Preferably, the cyclization reaction temperature is not higher than 250 °C. The cyclization may be carried out at a temperature not higher than 200 °C or at a temperature not higher than 180 °C.

For some embodiments, steps (1) and (3) of Reaction Scheme VIII are carried out as a one-pot procedure without isolating a compound of Formula VIII. The method may be carried out by adding an amine of formula R_1NH_2, or a suitable salt thereof, directly to the reaction mixture from step (1) of Reaction Scheme VIII. Optionally, the reaction mixture may be filtered prior to the addition of the amine of formula R_1NH_2. The resulting mixture can then be subjected to the conditions of step (3) to provide a compound of Formula I-H.

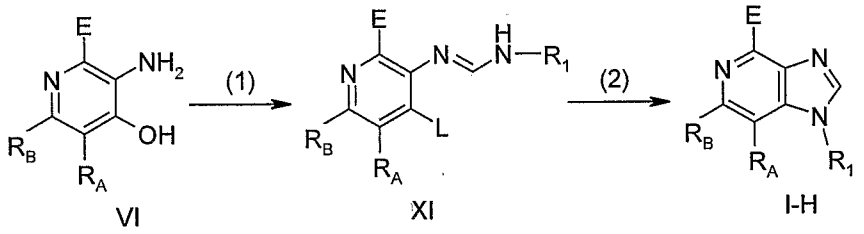
Reaction Scheme VIII



For certain embodiments, methods of the invention are shown Reaction Scheme IX, wherein R_A, R_B, R_1, E, and L are as defined above. In step (1) of Reaction Scheme IX, a 3-aminopyridine, 3-aminoquinoline, or 3-aminonaphthyridine of Formula VI is converted to an imidoformamide of Formula XI. Step (1) of Reaction Scheme IX may be carried out under the conditions described for step (1) of Reaction Scheme VIII using a formamide of formula HC(O)-NHR_1 instead of HC(O)-$N(R_{11})R_{12}$. Some formamides of formula HC(O)-NHR_1 are commercially available. Others can be prepared by known methods; for example, an amine of formula R_1NH_2 can be combined with a mixture of formic acid and acetic anhydride using any of the solvents and conditions described in step (1) of Reaction Scheme VIII in connection with the preparation of HC(O)-$N(R_{11})R_{12}$. Alternatively, an amine of formula R_1NH_2 can be combined with another formylating agent such as methyl formate, formamide, and chloroform in the presence of sodium hydroxide under to conditions known to one of skill in the art. See, for example, *J. Org. Chem.*, *23*, p. 1032 (1958), *J. Am. Chem. Soc. 78*, p. 2467 (1956), *J. Chem. Soc.*, p. 858 (1957), *J. Am. Chem. Soc. 74*, p. 5619 (1952), and *Tetrahedron Lett.*, *7*, p. 5 (1959). The compound of Formula XI may be isolated from the reaction mixture prior to step (2) of Reaction Scheme IX, or steps (1) and (2) may be carried out without isolating a compound of Formula XI.

If an imidoformamide of Formula XI is isolated, step (2) of Reaction Scheme IX can be used to cyclize a compound of Formula XI to a compound of Formula I-H. The reaction may be carried out neat at an elevated temperature such as the temperature required to melt the compound of Formula XI. The reaction may also be carried out in a suitable solvent at room temperature or at an elevated temperature. Suitable solvents include alcohols such as methanol, ethanol, trifluoroethanol, isopropanol, and *tert*-butanol; water; acetonitrile; NMP; and toluene. Preferred solvents include trifluoroethanol, isopropanol, *tert*-butanol, and acetonitrile. Preferably, the cyclization reaction temperature is not higher than 250 °C. The cyclization may be carried out at a temperature not higher than 200 °C or at a temperature not higher than 180 °C. Optionally, a base may be used in the reaction. Suitable bases include triethylamine. Optionally, a catalyst such as pyridine hydrochloride, pyridinium *p*-toluenesulfonate, or *p*-toluenesulfonic acid can be added.

Reaction Scheme IX



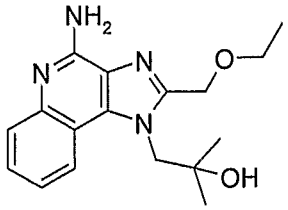
A compound of Formula I-H can be converted to a compound of Formula X, wherein R_2 is hydrogen, using a variety of methods, depending on the identity of E. Examples of these methods are shown in Reaction Schemes II through V, wherein R_2 is hydrogen. The synthetic methods of Reaction Schemes VI and VII can also be carried out using starting materials X_b and XXII wherein R_{2b} and R_2, respectively, are hydrogen.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Example 1

Preparation of 1-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol



Part A

Triethylamine (13.1 mL, 94.1 mmol) was added with stirring to a solution of 3-amino-4-chloroquinoline, see Surrey et al., *Journal of the American Chemical Society*, 73, pp. 2413-2416 (1951), (11.2 g, 62.7 mmol) in dichloromethane (125 mL). A solution of ethoxyacetyl chloride (9.2 g, 75 mmol) in dichloromethane (35 mL) was then added dropwise, and the reaction was stirred at room temperature overnight. An analysis by liquid chromatography/mass spectrometry (LC/MS) indicated the presence of starting material, and a solution of additional ethoxyacetyl chloride (2.3 g, 19 mmol) in dichloromethane (10 mL) was added dropwise. The reaction was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate (100 mL) was added, and the resulting mixture was stirred at room temperature for 30 minutes. The organic layer was separated and washed sequentially with saturated aqueous sodium bicarbonate (50 mL) and water (2 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 17.0 g of *N*-(4-chloroquinolin-3-yl)-2-ethoxyacetamide as a dark oil that crystallized upon standing.

Part B

A mixture of *N*-(4-chloroquinolin-3-yl)-2-ethoxyacetamide (4.5 g, 17 mmol), 1-amino-2-methylpropan-2-ol (2.3 g, 26 mmol), and *p*-toluenesulfonic acid monohydrate (150 mg, 0.79 mmol) was placed in a TEFLON-lined pressure vessel, heated at 125 °C for 15 hours, and allowed to cool to room temperature. Dichloromethane (150 mL) and saturated aqueous sodium bicarbonate (25 mL) were added, and the mixture was stirred for 15 minutes. The organic layer was separated and washed sequentially with saturated aqueous sodium bicarbonate (2 x 35 mL) and water (25 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 4.6 g of 1-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a dark brown oil.

HRMS (ESI) calcd for $C_{17}H_{21}N_3O_2$ M + H^+: 300.1712, found 300.1713.

Part C

A solution of 1-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (0.98 g, 3.3 mmol) in dichloromethane (35 mL) was cooled to approximately 0 °C, and 3-chloroperoxybenzoic acid (1.1 g of approximately 77% pure material, 5 mmol) was added. The reaction was stirred for ten minutes at 0 °C, stirred for three hours at room temperature, diluted with dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (35 mL), and stirred for 15 minutes. The aqueous layer was separated and extracted with dichloromethane (3 x 25 mL), and the combined organic fractions were dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 0.96 g of 1-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a brown oil.

HRMS (ESI) calcd for $C_{17}H_{21}N_3O_3$ M+ H^+: 316.1661, found 316.1664.

Part D

A solution of 1-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (0.96 g, 3.0 mmol) in dichloromethane (35 mL) was cooled to 0 °C, and trichloroacetyl isocyanate (0.60 mL, 5.0 mmol) was added with stirring. The reaction was stirred for 15 minutes at 0 °C and then stirred overnight at room temperature. Methanol (10 mL) was added, and the mixture was stirred for 15 minutes and concentrated under reduced pressure. The residue was dissolved in methanol (10 mL), and sodium methoxide (0.25 mL of a 25% w/w solution in methanol) was added. The mixture was stirred at room temperature for three hours. An analysis by LC/MS indicated the reaction was incomplete, and additional sodium methoxide solution (1.0 mL) was added. The reaction was stirred overnight at room temperature and determined to be incomplete. Hydrochloric acid (5 mL of 10% w/w) was added, and the mixture was stirred for one hour. Saturated aqueous sodium bicarbonate (15 mL) and aqueous sodium hydroxide (ten drops of 50% w/w) were added, and the reaction was stirred overnight at room temperature. An analysis by LC/MS again showed that the reaction was incomplete. Potassium hydroxide (5 mL of a 0.5 N solution in methanol) was added, and the reaction mixture was heated at reflux for four hours, allowed to cool to room temperature, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (75 mL), and the solution was washed with water (2 x 50 mL), dried over potassium

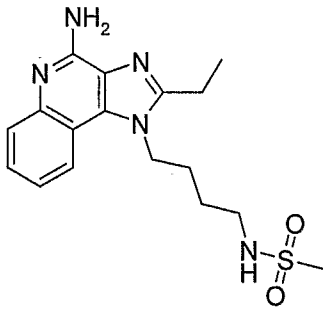
carbonate, filtered, and concentrated under reduced pressure. The residue (0.64 g) was purified by column chromatography on silica gel (eluting with 5% methanol in dichloromethane containing 2 mL of aqueous ammonium hydroxide per liter of eluent). The resulting solid was recrystallized from methanol/water, recrystallized three times from methanol, and dried overnight under vacuum at 70 °C to provide 1-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as tan needles, mp 192-194 °C.

MS (APCI) *m/z* 315 ($M + H^+$); HRMS (ESI) calcd for $C_{17}H_{22}N_4O_2$ M+ H^+: 315.1821, found 315.1819.

Anal. calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82. Found: C, 64.94; H, 6.94; N, 17.74.

Example 2

Preparation of *N*-[4-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide



Part A

A solution of 3-amino-4-chloroquinoline (5.0 g, 28 mmol) and triethylamine (5.8 mL, 42 mmol) in dichloromethane (100 mL) was cooled to approximately 0 °C. A solution of propionyl chloride (2.8 g, 31 mmol) in dichloromethane (15 mL) was then added dropwise over a period of 15 minutes, and the reaction was allowed to warm to room temperature and stirred overnight. An analysis by high performance liquid chromatography (HPLC) indicated the presence of starting material, and additional triethylamine (1.95 mL, 14.0 mmol) and propionyl chloride (0.85 g, 9.2 mmol) in dichloromethane (5 mL) were added. The reaction was stirred at room temperature overnight; diluted with dichloromethane (100 mL); washed sequentially with water, saturated aqueous sodium carbonate, 10% w/w aqueous sodium hydroxide, saturated

aqueous sodium carbonate, and brine; dried over magnesium sulfate and sodium sulfate, filtered, and concentrated under reduced pressure. The resulting brown solid (8.1 g) was recrystallized from toluene to provide 4.5 g of *N*-(4-chloroquinolin-3-yl)propanamide as beige platelets, mp 151-152 °C.

Part B

In a glass-lined pressure vessel, a solution of *N*-(4-chloroquinolin-3-yl)propanamide (3.3 g, 14 mmol), *N*-(4-aminobutyl)methanesulfonamide hydrochloride (see Example 199 in U. S. Patent Application Publication No. 2004/0147543, 3.14 g, 15.5 mmol), and triethylamine (3.9 mL, 28 mmol) in trifluoroethanol (35 mL) was heated at 150 °C for 16 hours and allowed to cool to room temperature. The volatiles were removed under reduced pressure, and the resulting amber paste was dissolved in dichloromethane. The solution was washed sequentially with dilute aqueous ammonium chloride, saturated aqueous sodium carbonate (2 x), and brine; dried over magnesium sulfate and sodium sulfate; filtered; and concentrated under reduced pressure. The resulting amber syrup (4.8 g) was recrystallized from hot propyl acetate. The crystals were washed with propyl acetate to provide 3.8 g of *N*-[4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide as light amber granules, mp 166-168 °C.

Part C

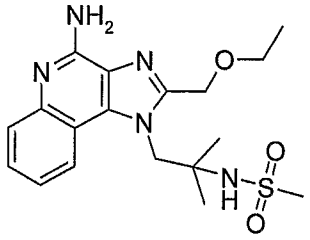
Solid 3-chloroperoxybenzoic acid (2.7 g of approximately 77% pure material, 13 mmol) was added in portions to a solution of *N*-[4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide (3.8 g, 11 mmol) in dichloromethane (75 mL). The reaction was stirred for five hours at room temperature. An analysis by HPLC indicated the presence of starting material, and additional 3-chloroperoxybenzoic acid (0.5 g) was added. The reaction was stirred for one hour at room temperature, and ammonium hydroxide (50 mL) was added. The resulting mixture was vigorously stirred at room temperature for 15 minutes, and then *p*-toluenesulfonyl chloride (2.5 g, 0.013 mol) was added in one portion. The mixture was stirred vigorously at room temperature overnight. A fine solid was present and was collected by vacuum filtration (3.4 g) and recrystallized from ethanol (100 mL). The crystals were dried in a vacuum oven at 60 °C for four hours to provide 3.0 g of *N*-[4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide as straw-colored, feathery crystals, m.p. 198-200 °C.

MS (APCI) *m/z* 362 $(M + H)^+$;

Anal. calcd for $C_{17}H_{23}N_5O_2S$: C, 56.49; H, 6.41; N, 19.37. Found: C, 56.31; H, 6.49; N, 19.13.

Example 3

Preparation of *N*-{2-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide monohydrate



Part A

A solution of 1,2-diamino-2-methylpropane (11.9 mL, 113 mmol), *tert*-butyl phenyl carbonate (42.1 mL, 227 mmol) and absolute ethanol (500 mL) was heated at reflux under a nitrogen atmosphere for 20.5 hours. The volatiles were removed under reduced pressure, and the residue was dissolved in water (560 mL). The solution was adjusted to approximately pH 3 with the addition of hydrochloric acid (140 mL of 1 N) and washed with dichloromethane (2 x 1 L). The aqueous solution was then adjusted to approximately pH 12 with the addition of aqueous sodium hydroxide (70 mL of 2 N) and extracted with dichloromethane (5 x 800 mL). The combined extracts were dried over sodium sulfate, filtered, concentrated under reduced pressure, and further dried under vacuum to provide 13.05 g of *tert*-butyl 2-amino-2-methylpropylcarbamate, which was combined with material from other runs.

Part B

A solution of *tert*-butyl 2-amino-2-methylpropylcarbamate (20.8 g, 111 mmol) and triethylamine (23.2 mL, 167 mmol) in dichloromethane (125 mL) was cooled to –9 °C. A solution of methanesulfonic anhydride (21.25 g, 122 mmol) in dichloromethane (106 mL) was added over a period of 50 minutes while maintaining the reaction temperature at or below –4 °C. After the addition, the reaction was stirred for 30 minutes; diluted with dichloromethane (80 mL); washed sequentially with brine (30 mL), saturated aqueous ammonium chloride (30 mL), 10% w/w hydrochloric acid (20 mL), brine (10 mL), saturated aqueous sodium carbonate (20 mL), and brine (10 mL); dried over magnesium

sulfate, filtered, concentrated under reduced pressure, and dried under vacuum to provide *tert*-butyl 2-methyl-2-[(methylsulfonyl)amino]propylcarbamate.

Part C

Hydrogen chloride (153 mL of a 4 N solution in 1,4-dioxane) was cooled to 0 °C and stirred. The material from Part B was added in portions followed by an ethanol rinse. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the residue was concentrated twice from ethanol and dried under vacuum to provide *N*-(2-amino-1,1-dimethylethyl)methanesulfonamide hydrochloride.

Part D

In a glass-lined pressure vessel, a solution of *N*-(4-chloroquinolin-3-yl)-2-ethoxyacetamide (2.0 g, 7.6 mmol), *N*-(2-amino-1,1-dimethylethyl)methanesulfonamide hydrochloride (2.16 g, 10.7 mmol), and triethylamine (2.6 mL, 19 mmol) in trifluoroethanol (30 mL) was heated at 150 °C for 16 hours. An analysis by HPLC indicated the presence of starting material, and additional *N*-(2-amino-1,1-dimethylethyl)methanesulfonamide hydrochloride (0.5 g) and triethylamine (0.3 mL) were added. The heating was continued for an additional 16 hours. The volatiles were removed under reduced pressure, and the resulting amber paste was dissolved in dichloromethane. The solution was washed sequentially with dilute aqueous ammonium chloride, saturated aqueous sodium carbonate (2 x), and brine; dried over magnesium sulfate and sodium sulfate; filtered; and concentrated under reduced pressure. The resulting amber syrup (4 g) was purified by column chromatography on silica gel to provide 1.6 g of *N*-{2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide as an amber syrup.

Part E

Solid 3-chloroperoxybenzoic acid (1.1 g of approximately 77% pure material, 5 mmol) was added in portions to a solution of *N*-{2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide (1.6 g, 4.2 mmol) in dichloromethane (30 mL). The reaction was stirred for three hours at room temperature. An analysis by HPLC indicated the presence of a small amount of starting material, and additional 3-chloroperoxybenzoic acid (0.2 g) was added. The reaction was stirred for one hour at room temperature, and ammonium hydroxide (30 mL) was added. The resulting

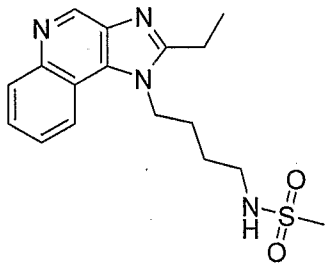
mixture was vigorously stirred at room temperature for 15 minutes, and then *p*-toluenesulfonyl chloride (0.97 g, 0.0051 mol) was added in one portion. The reaction mixture was vigorously stirred at room temperature for two hours, diluted with dichloromethane, washed sequentially with saturated aqueous sodium carbonate (2 x) and brine (1 x), dried over sodium sulfate and magnesium sulfate, filtered, and concentrated under reduced pressure to give an amber syrup. The syrup was purified by column chromatography on silica gel (eluting with dichloromethane) followed by recrystallization from propyl acetate (10 mL/g) to give 0.8 g of a tan solid. The solid was recrystallized from ethanol (4 mL) and water (two drops), and the crystals were dried in a vacuum oven at 60 °C for four hours to provide 0.55 g of *N*-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide monohydrate as pale yellow crystals, m.p. 161-163 °C.

MS (ESI) *m/z* 392 $(M + H)^+$;

Anal. calcd for $C_{18}H_{25}N_5O_3S \cdot 1.0\ H_2O$: C, 52.79; H, 6.65; N, 17.10. Found: C, 52.69; H, 6.56; N, 16.87.

Example 4

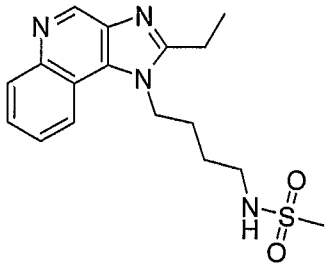
Preparation of *N*-[4-(2-Ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide



A mixture of *N*-(4-chloroquinolin-3-yl)propanamide (0.1 g, 0.4 mmol) and *N*-(4-aminobutyl)methanesulfonamide hydrochloride (0.095 g, 0.5 mmol) was sealed in a vial, heated at 125 °C for 16 hours, and allowed to cool to room temperature. Water was added, and the solution was adjusted to approximately pH 10 with the addition of sodium carbonate. The aqueous solution was extracted twice with dichloromethane (50 mL), and the combined extracts were washed with brine, dried over magnesium sulfate and sodium sulfate, filtered, and concentrated under reduced pressure. Analysis by HPLC and mass spectrometry gave evidence that *N*-[4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide was the major product. MS (APCI) *m/z* 347 $(M + H)^+$.

Examples 5 and 6

Preparation of *N*-[4-(2-Ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide

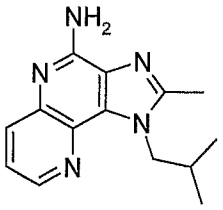


A solution of *N*-(4-chloroquinolin-3-yl)propanamide (0.05 g, 0.2 mmol), *N*-(4-aminobutyl)methanesulfonamide hydrochloride (0.047 g, 0.2 mmol), and triethylamine (0.059 mL, 0.40 mmol) in the solvent indicated below was sealed in a vial and heated at 128 °C for 48 hours. An analysis by HPLC indicated the ratio of *N*-[4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide to *N*-(4-chloroquinolin-3-yl)propanamide shown below.

Example	Solvent	Product:Starting Material
5	*tert*-butanol	93:7
6	isopropanol	92:8

Example 7

Preparation of 2-Methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

A Parr vessel was flushed with nitrogen and charged with 5% platinum on carbon (1.1 g) and water (5 mL). A solution of 3-nitro[1,5]naphthyridin-4-ol (22.0 g, 0.115 mol) in triethylamine (23.3 g, 0.230 mol) and water (1.1 L) was added, and the mixture was placed under hydrogen pressure (35 psi, 2.4 x 10^5 Pa) for three hours and then filtered through a layer of CELITE filter agent. The filtrate was concentrated to a volume of 400 mL by flash evaporation at 75 °C and allowed to cool. A solid formed and was collected

by vacuum filtration to give 3-amino[1,5]naphthyridin-4-ol (16.4 g) as a fine mustard-colored powder, mp 315-320 °C.

MS (ESI) *m/z* 162 $(M + H)^+$.

Part B

Phosphorus(III) oxychloride (47.0 g, 0.304 mol) was added dropwise over a period of 30 minutes to a mixture of 3-amino[1,5]naphthyridin-4-ol (20.0 g, 0.124 mol) in *N,N*-dimethylformamide (DMF) (200 mL); the reaction temperature was maintained between 10 °C and 20 °C during the addition. When the addition was complete, the reaction was stirred at room temperature for three hours, heated to 90 °C for 15 minutes, and allowed to cool to room temperature. Water (150 mL) and ice were added while maintaining the temperature below 55 °C. The mixture was stirred at room temperature for 30 minutes, heated at 100 °C for three hours, and allowed to cool to room temperature overnight. The resulting black solution was made basic by slowly adding solid sodium carbonate and saturated aqueous sodium carbonate. The basic solution was extracted three times with dichloromethane. The combined extracts were washed with brine, dried over sodium sulfate and magnesium sulfate, and concentrated under reduced pressure to give a sticky amber paste. The paste was triturated with warm diethyl ether for 30 minutes, and the resulting solid was collected by vacuum filtration to give 4-chloro[1,5]naphthyridin-3-amine (11 g) as brown granules, mp 188-190 °C.

MS (ESI) *m/z* 180 $(M + H)^+$.

Part C

A solution of 4-chloro[1,5]naphthyridin-3-amine (4.0 g, 0.022 mol) and triethylamine (4.6 mL, 0.033 mol) in 1,2-dichloroethane (80 mL) was cooled to 3 °C. A solution of acetyl chloride (4.4 g, 0.056 mol) in 1,2-dichloroethane (5 mL) was added dropwise over a period of five minutes. The reaction was then heated at reflux for five hours; allowed to cool to room temperature; diluted with dichloromethane (100 mL); washed sequentially with saturated aqueous sodium carbonate (2 x), water (1 x), and brine (1 x); dried over sodium sulfate and magnesium sulfate; filtered; and concentrated under reduced pressure to give 4.7 g of dark brown solid. The solid was recrystallized from acetonitrile (20 mL) and collected in two crops to give *N*-(4-chloro[1,5]naphthyridin-3-yl)acetamide (3.0 g) as brown solids.

MS (ESI) *m/z* 222 $(M + H)^+$.

Part D

A mixture of *N*-(4-chloro[1,5]naphthyridin-3-yl)acetamide (1.6 g, 0.073 mol) and isobutylamine (7.3 mL, 0.0722 mol) was heated in a sealed vial at 120 °C overnight, allowed to cool to room temperature, and added to a solution of water (100 mL) and saturated aqueous sodium carbonate (20 mL). A precipitate formed. The mixture was stirred at room temperature for 1.5 hours, and the precipitate was collected by vacuum filtration and dried on the filter funnel to give 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (1.45 g) as gray powder, mp 110-111 °C.

MS (APCI) *m/z* 241 $(M + H)^+$.

Part E

Solid 3-chloroperoxybenzoic acid (1.8 g of approximately 77% pure material, 0.0078 mol) was added in portions to a solution of 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (1.45 g, 0.0060 mol) in dichloromethane (30 mL). The reaction was stirred at room temperature for three hours and washed with saturated aqueous sodium carbonate (100 mL). The aqueous fraction was extracted three times with dichloromethane. The combined organic fractions were washed with brine, dried over sodium sulfate and magnesium sulfate, filtered, and concentrated under reduced pressure to give 2-methyl-1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (1.3 g) as yellow solid.

MS (APCI) *m/z* 257 $(M + H)^+$.

Part F

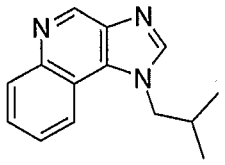
p-Toluenesulfonyl chloride (1.2 g, 0.0061 mol) was added to a vigorously stirred mixture of 2-methyl-1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (1.3 g, 0.0051 mol), dichloromethane (25 mL), and ammonium hydroxide (17 mL). The reaction was vigorously stirred at room temperature for two hours, and then the stirring was stopped and the layers allowed to separate for two hours. A precipitate formed and was collected by vacuum filtration to give 0.9 g of ivory needles. The needles were recrystallized from isopropanol (12 mL), and the collected crystals were dried in a vacuum oven at 60 °C for five hours to give 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.7 g) as colorless needles, mp 227-229 °C.

MS (ESI) *m/z* 256 $(M + H)^+$;

Anal. calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.53; H, 6.68; N, 27.35.

Example 8

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline



Part A

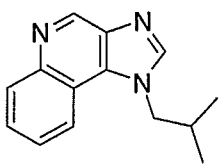
Formic acid (0.36 mL) was slowly added with stirring to acetic anhydride (0.8 mL), and the reaction was stirred at room temperature for 2.75 hours and then added to a solution of 3-amino-4-chloroquinoline (0.50 g, 2.8 mmol) in tetrahydrofuran (5 mL). The resulting mixture was stirred for one hour at room temperature. A solid was present and was collected by filtration and washed with diethyl ether to provide 0.48 g of 4-chloroquinolin-3-ylformamide as a beige solid, mp 175-177 °C.

Part B

A mixture of 4-chloroquinolin-3-ylformamide (0.050 g, 0.24 mol) and isobutylamine (0.25 mL, 2.4 mmol) was heated in a sealed vial at 110 °C overnight and allowed to cool to room temperature. Dichloromethane (1 mL) and aqueous ammonium chloride (1 mL of 10% w/w) were added. The organic layer was separated and washed with 10% w/w aqueous ammonium chloride, dried over sodium sulfate, concentrated under reduced pressure, and dried overnight in a vacuum oven at 35 °C to provide 41 mg of a brown crystalline solid that was analyzed by LC/MS and found to be a mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline and 3-amino-4-chloroquinoline.

Example 9

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline



Part A

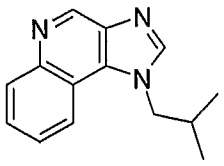
Phosphorous oxychloride (90 mL, 0.97 mol) was added dropwise to a stirred slurry of 3-aminoquinolin-4-ol hydrochloride (150 g, 0.76 mol) in 500 mL of DMF. The temperature of the mixture increased to about 100 °C over the course of the addition. The reaction mixture was allowed to cool to room temperature, then about two-thirds of the DMF was removed under reduced pressure. The mixture was then filtered and the solid dried to provide *N'*-(4-chloroquinolin-3-yl)-*N*,*N*-dimethylimidoformamide (118 g), MS (ESI) *m/z* 234 $(M + H)^+$.

Part B

A glass vial was charged with *N'*-(4-chloroquinolin-3-yl)-*N*,*N*-dimethylimidoformamide (0.10 g, 0.40 mmol), isobutylamine (0.50 mL, 5.4 mmol), and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol). The vial was placed inside a steel pressure reactor and the vessel heated in an oven at 150 °C for 15 hours. After cooling to room temperature, examination of the reaction mixture by liquid chromatography/mass spectrometry indicated that the reaction was incomplete, so the vessel was placed back inside the oven and heated at 175 °C for 15 hours. After cooling to room temperature, examination of the reaction mixture by liquid chromatography/mass spectrometry indicated that the major product of the reaction was 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline, MS (ESI) *m/z* 226 $(M + H)^+$.

Example 10

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline



A flask was charged with 3-aminoquinolin-4-ol hydrochloride (1.0 g, 5.1 mmol), 20 mL of acetonitrile and 1.5 mL of DMF. Phosphorous oxychloride (0.7 mL, 7.5 mmol) was added to the stirred slurry. The mixture was stirred at ambient temperature for 21 hours. The mixture was filtered to remove solids, rinsing with acetonitrile. To the filtrates was added isobutylamine (2.5mL, 25.5 mmol). An exotherm was observed upon addition and the solution became a slurry. The mixture was placed in a glass pressure vessel and

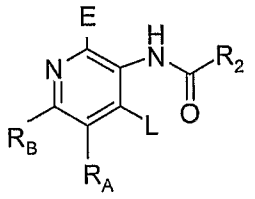
heated in an oven at 120 °C for 3 hours. After cooling to room temperature, examination of the reaction mixture by liquid chromatography/mass spectrometry indicated that the reaction was mainly complete. The slurry was taken up in 50 mL of water and 50 mL of dichloromethane. The layers were separated. The aqueous was extracted with 25 mL of dichloromethane, which was combined with the separated dichloromethane layer. Examination of the combined dichloromethane layers by liquid chromatography/mass spectrometry indicated that the major product was 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline, MS (ESI) *m/z* 226 $(M + H)^+$. The layers were dried with magnesium sulfate, filtered and concentrated to provide 0.17 g (15%) of a sticky amber residue. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.43 (s, 1H), 8.35 (m, 1H), 8.18 (m, 1H), 7.74 (m, 2H), 4.53 (d, J = 7.5 Hz, 2H), 2.22 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H); HRMS (ESI) calcd for $C_{14}H_{15}N_3$ $[M+ H]^+$: 226.1344, found 226.1352.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

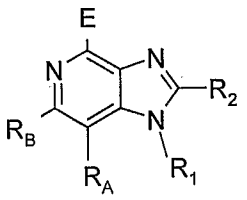
1. A method for preparing a 1*H*-imidazo[4,5-*c*]pyridine compound or analog thereof or a pharmaceutically acceptable salt thereof comprising:

providing a compound of the Formula IV:



IV

and reacting the compound of Formula IV with an amine of the formula R_1NH_2 to provide a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:



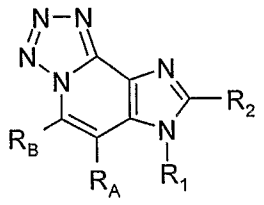
I

or a pharmaceutically acceptable salt thereof;

wherein:

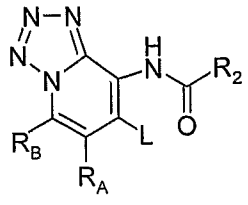
E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formulas I and IV to form the fused tetrazolo ring in Formulas I-1 and IV-1:



I-1

and



IV-1;

L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,
-X-R_4,
-X-Y-R_4,
-X-Y-X-Y-R_4,
-X-R_5,

$-N(R_1')-Q-R_4$,

$-N(R_1')-X_1-Y_1-R_4$, and

$-N(R_1')-X_1-R_{5b}$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X_1 is C_{2-20} alkylene;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-O-C(R_6)-N(R_8)-$,

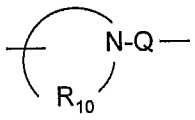
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

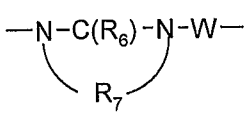
$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

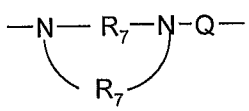
-CH(-N(-O-R_8)-Q-R_4)-,



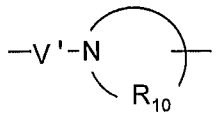
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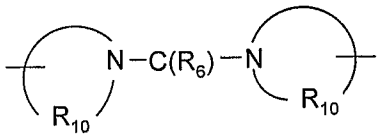
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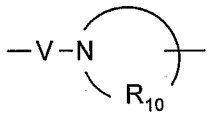
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, and



;

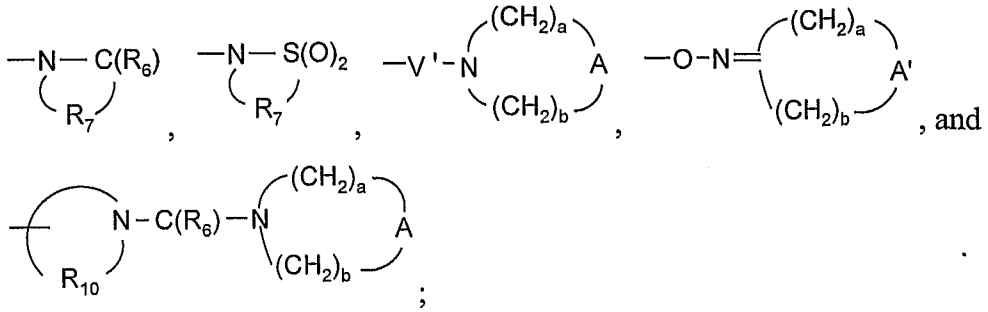
Y_1 is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, and ;

Z is a bond or -O-;

R_1' is selected from the group consisting of hydrogen, C_{1-20} alkyl, hydroxy-C_{2-20} alkylenyl, and alkoxy-C_{2-20} alkylenyl;

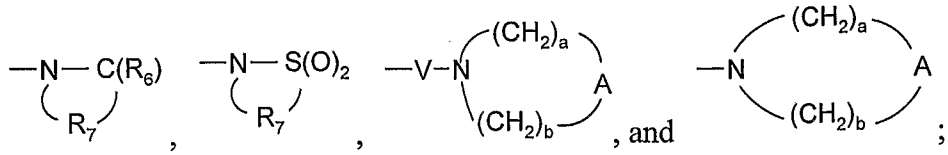
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_{5b} is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

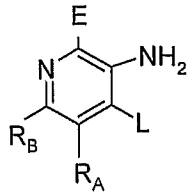
V' is selected from the group consisting of $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

2. The method of claim 1 further comprising the steps of:

providing a compound of the Formula III:

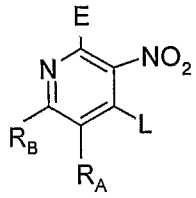


III

and reacting the compound of Formula III with a carboxylic acid halide of the formula hal-C(O)-R_2, wherein hal is chloro or bromo, or an anhydride or mixed anhydride of the formula O(-C(O)-R_2)$_2$ to provide an compound of Formula IV.

3. The method of claim 2 further comprising the steps of:

providing a compound of the Formula II:

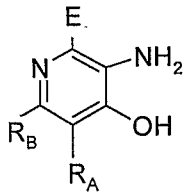


II

and reducing the compound of Formula II to provide a compound of Formula III.

4. The method of claim 2 further comprising the steps of:

providing a compound of the Formula VI:

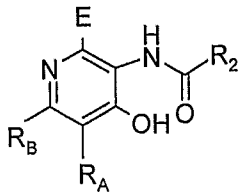


VI

and converting the hydroxy group at the 4-position of Formula VI to an L group to provide a compound of Formula III.

5. The method of claim 1 further comprising the steps of:

providing a compound of the Formula VII:

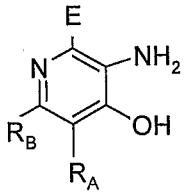


VII

and converting the hydroxy group at the 4-position of Formula VII to an L group to provide a compound of Formula IV.

6. The method of claim 5 further comprising the steps of:

providing a compound of the Formula VI:

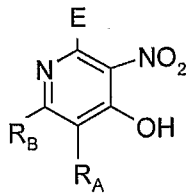


VI

and reacting the compound of Formula VI with a carboxylic acid halide of the formula hal-C(O)-R_2, wherein hal is a chloro or bromo, or an anhydride or mixed anhydride of the formula O(-C(O)-R_2)$_2$ to provide an compound of Formula VII.

7. The method of claim 4 or 6 further comprising the steps of:

providing a compound of the Formula V:

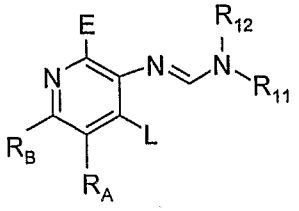


V

and reducing the compound of Formula V to provide a compound of Formula VI.

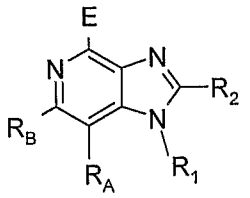
8. A method for preparing a 1*H*-imidazo[4,5-*c*]pyridine compound or analog thereof or a pharmaceutically acceptable salt thereof comprising:

providing a compound of the Formula VIII:



VIII

and reacting the compound of Formula VIII with an amine of the formula R_1NH_2 to provide a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:



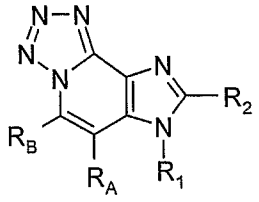
I

or a pharmaceutically acceptable salt thereof;

wherein:

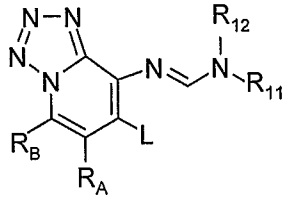
E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formulas I and VIII to form the fused tetrazolo ring in Formulas I-1 and IX:



I-1

and



IX;

L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$,
$-X-Y-X-Y-R_4$,
$-X-R_5$,
$-N(R_1')-Q-R_4$,
$-N(R_1')-X_1-Y_1-R_4$, and
$-N(R_1')-X_1-R_{5b}$;

R_2 is hydrogen;

R_3 is selected from the group consisting of:

$-Z-R_4$,

-Z-X-R_4,

-Z-X-Y-R_4,

-Z-X-Y-X-Y-R_4, and

-Z-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X_1 is C_{2-20} alkylene;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-$N(R_8)$-Q-,

-O-$C(R_6)$-$N(R_8)$-,

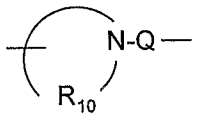
-$C(R_6)$-$N(OR_9)$-,

-O-$N(R_8)$-Q-,

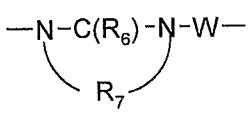
-O-N=$C(R_4)$-,

-C(=N-O-R_8)-,

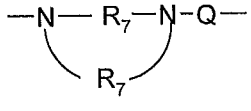
-CH(-N(-O-R_8)-Q-R_4)-,



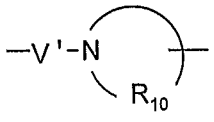
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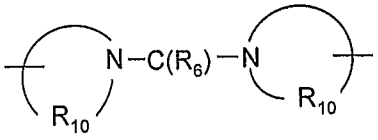


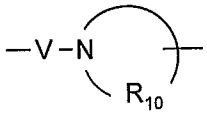
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,


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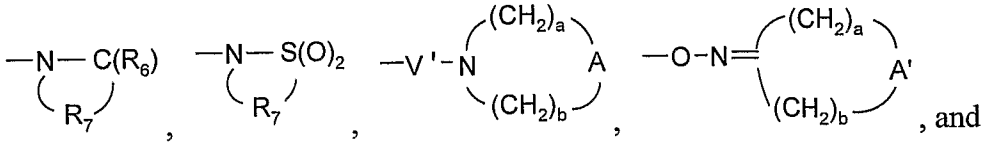
Y_1 is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, and 
;

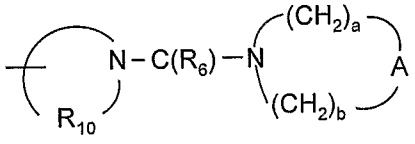
Z is a bond or -O-;

R_1' is selected from the group consisting of hydrogen, C_{1-20} alkyl, hydroxy-C_{2-20} alkylenyl, and alkoxy-C_{2-20} alkylenyl;

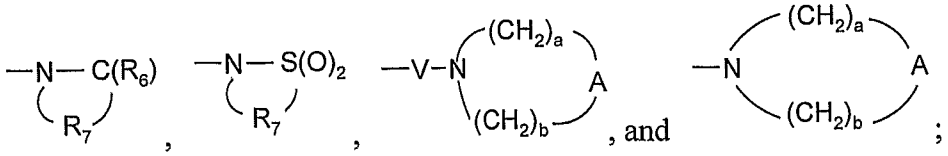
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


, and


;

R_{5b} is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} and R_{12} are independently C_{1-4} alkyl or R_{11} and R_{12} together with the nitrogen atom to which they are attached form a 5- or 6-membered ring optionally containing -O-, $-N(C_{1-4}$ alkyl)-, or -S-;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, $-C(R_6)-S$-, and $-C(R_6)-N(OR_9)$-;

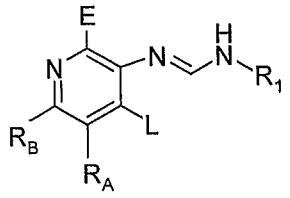
V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

V' is selected from the group consisting of $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$.

9. The method of claim 8 further comprising forming an intermediate of Formula XI:



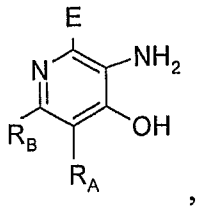
XI

after reacting the compound of Formula VIII with an amine of the formula R_1NH_2.

10. The method of claim 9 wherein the intermediate of Formula XI is isolated after reacting the compound of Formula VIII with an amine of the formula R_1NH_2.

11. The method of claim 8 or claim 9 further comprising:

providing a compound of the Formula VI:



VI

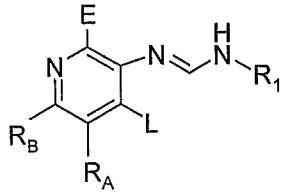
converting the hydroxy group at the 4-position to an L group,

and reacting the amino group at the 3-position with a formamide of the formula H-C(O)-N(R_{11})R_{12} to provide a compound of Formula VIII.

12. The method of claim 11 wherein the compound of Formula VIII is provided without being isolated prior to reacting with an amine of the formula R_1NH_2.

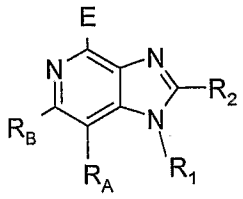
13. A method for preparing a 1*H*-imidazo[4,5-*c*]pyridine compound or analog thereof or a pharmaceutically acceptable salt thereof comprising:

providing a compound of the Formula XI:



XI

and forming a 1*H*-imidazo[4,5-*c*]pyridine or analog thereof of the Formula I:



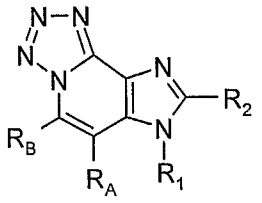
I

or a pharmaceutically acceptable salt thereof;

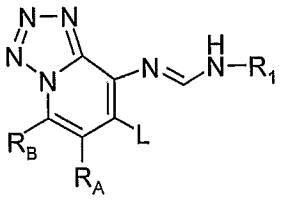
wherein:

E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formulas I and XI to form the fused tetrazolo ring in Formulas I-1 and XIII:



and



I-1 XIII;

L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_1 is selected from the group consisting of:
$-R_4$,
$-X-R_4$,
$-X-Y-R_4$,
$-X-Y-X-Y-R_4$,
$-X-R_5$,
$-N(R_1')-Q-R_4$,
$-N(R_1')-X_1-Y_1-R_4$, and
$-N(R_1')-X_1-R_{5b}$;

R_2 is hydrogen;

R_3 is selected from the group consisting of:
$-Z-R_4$,
$-Z-X-R_4$,
$-Z-X-Y-R_4$,
$-Z-X-Y-X-Y-R_4$, and
$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X_1 is C_{2-20} alkylene;

Y is selected from the group consisting of:
-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-O-C(R_6)-N(R_8)-,

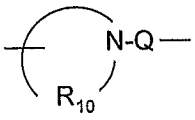
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

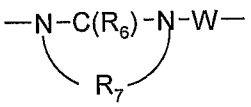
-O-N=C(R_4)-,

-C(=N-O-R_8)-,

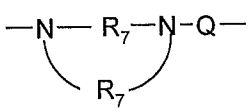
-CH(-N(-O-R_8)-Q-R_4)-,



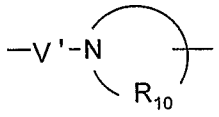
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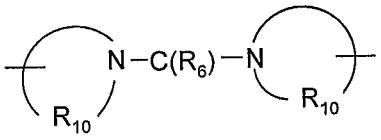
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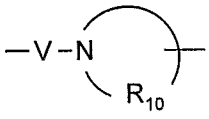
,



, and



;

Y_1 is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, and 

;

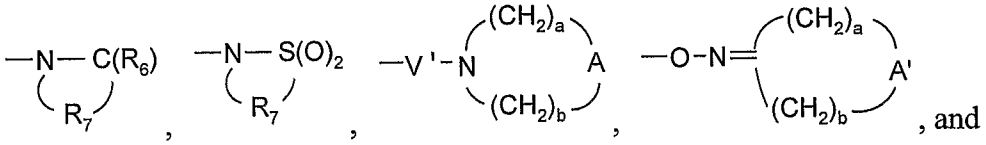
Z is a bond or -O-;

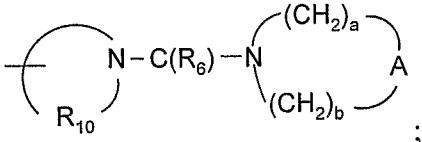
R_1' is selected from the group consisting of hydrogen, C_{1-20} alkyl, hydroxy-C_{2-20} alkylenyl, and alkoxy-C_{2-20} alkylenyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

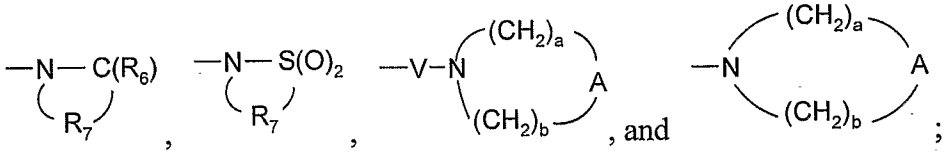
alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


, and


;

R_{5b} is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

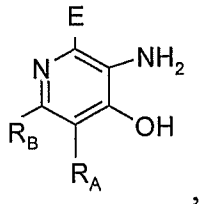
V' is selected from the group consisting of $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

14. The method of claim 13 further comprising:

providing a compound of the Formula VI:



VI

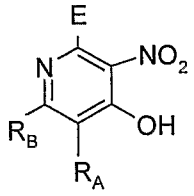
converting the hydroxy group at the 4-position to an L group,

and reacting the amino group at the 3-position with a formamide of the formula H-C(O)-NH(R_1) to provide a compound of Formula XI.

15. The method of claim 14 wherein the compound of Formula XI is provided without being isolated prior to forming a compound of Formula I.

16. The method of any one of claims 11, 12, 14, and 15 further comprising:

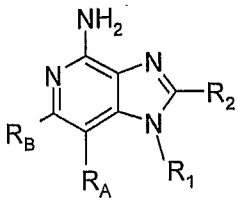
providing a compound of the Formula V:



V

and reducing the compound of Formula V to provide a compound of Formula VI.

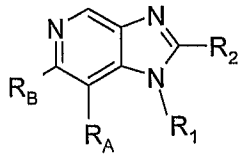
17. The method of any one of claims 1 through 16 further comprising the step of converting E to an amino group in the compound of Formula I to provide a compound of the Formula X:



X,

or a pharmaceutically acceptable salt thereof.

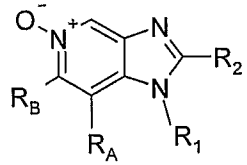
18. The method of claim 17 wherein E is hydrogen, the compound of Formula I is the Formula I-2:



I-2,

and the step of converting the hydrogen to an amino group in the compound of Formula I-2 comprises:

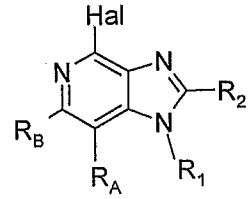
oxidizing the compound of Formula I-2 to provide a the 5*N*-oxide of Formula XX:



XX,

and aminating the compound of Formula XX to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

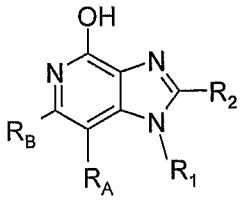
19. The method of claim 17 wherein E is Hal, and the compound of Formula I is the Formula I-3:



I-3

wherein Hal is fluoro, chloro, bromo, or iodo, and the step of converting the Hal group to an amino group in the compound of Formula I-3 comprises aminating the compound of Formula I-3 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

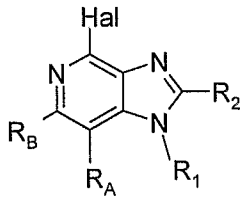
20. The method of claim 17 wherein E is hydroxy, the compound of Formula I is the Formula I-4:



I-4,

and the step of converting the hydroxy group to an amino group in the compound of Formula I-4 comprises:

converting the hydroxy group at the 4-position of Formula I-4 to a halo group to provide a compound or salt of Formula I-3:

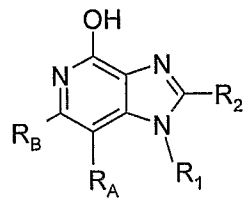


I-3

wherein Hal is fluoro, chloro, bromo, or iodo; and

aminating the compound of Formula I-3 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

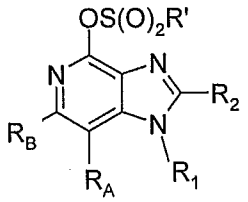
21. The method of claim 17 wherein E is hydroxy, the compound of Formula I is the Formula I-4:



I-4,

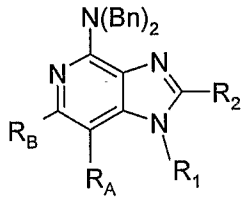
and the step of converting the hydroxy group to an amino group in the compound of Formula I-4 comprises:

sulfonating the compound of Formula I-4 by reaction with a compound of the formula hal-$S(O)_2$-R' wherein hal is chloro or bromo, or the formula $O(-S(O)_2-R')_2$, to provide a compound of the Formula I-5:



I-5

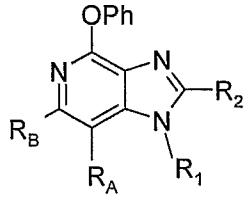
displacing the -O-$S(O)_2$-R' group in Formula I-5 by an amino group of the formula -$N(Bn)_2$ to provide a compound of the Formula I-6:



I-6

removing the Bn protecting groups in Formula I-6 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

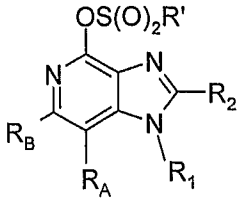
22. The method of claim 17 wherein E is phenoxy, and the compound of Formula I is the Formula I-7:



I-7,

wherein Ph is phenyl, and the step of converting the phenoxy group to an amino group in the compound of Formula I-7 comprises aminating the compound of Formula I-7 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

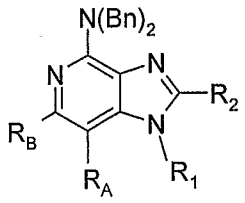
23. The method of claim 17 wherein E is -O-S(O)$_2$-R', the compound of Formula I is the Formula I-5:



I-5,

and the step of converting the -O-S(O)$_2$-R' group to an amino group in the compound of Formula I-5 comprises:

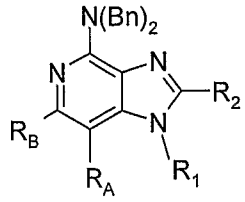
displacing the -O-S(O)$_2$-R' group by an amino group of the formula -N(Bn)$_2$ to provide a compound of the Formula I-6:



I-6

and removing the Bn protecting groups in Formula I-6 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

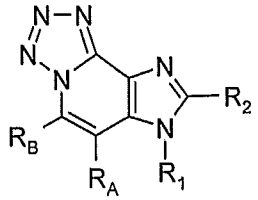
24. The method of claim 17 wherein E is -N(Bn)$_2$, the compound of Formula I is the Formula I-6:



I-6,

and the step of converting the -N(Bn)$_2$ group to an amino group in the compound of Formula I-6 comprises removing the Bn protecting groups to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

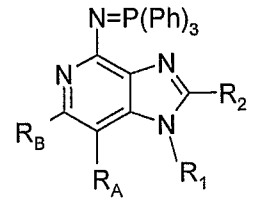
25. The method of claim 17 wherein E is joined with the adjacent pyridine nitrogen atom of Formula I to form the fused tetrazolo ring in Formula I-1:



I-1,

and the step of converting the fused tetrazolo ring to an amino group in the compound of Formula I-1 comprises the steps of:

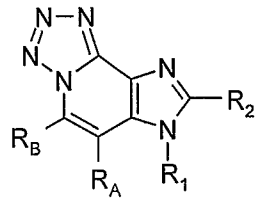
reacting the compound of Formula I-1 with triphenylphosphine to provide a compound of the Formula XXI:



XXI

and hydrolyzing the compound of Formula XXI to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

26. The method of claim 17 wherein E is joined with the adjacent pyridine nitrogen atom of Formula I to form the fused tetrazolo ring in Formula I-1:



I-1,

and the step of converting the fused tetrazolo ring to an amino group in the compound of Formula I-1 comprises the step of:

reductively removing the tetrazolo ring from the compound of Formula I-1 to provide the compound of Formula X, or a pharmaceutically acceptable salt thereof.

27. The method of any one of claims 1 through 7 or any one of claims 17 through 26 as dependent on any one of claims 1 through 7 wherein R_2 is $-R_4$.

28. The method of claim 27 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, ethoxymethyl, and hydroxymethyl.

29. The method of any one of claims 1 through 28 wherein R_1 is $-R_4$ or $-X-R_4$.

30. The method of claim 29 wherein $-R_4$ is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,2-dimethyl-4-oxopentyl, and (1-hydroxycyclobutyl)methyl, and $-X-R_4$ is 2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl.

31. The method of claim 30 wherein $-R_4$ is 2-methylpropyl.

32. The method of any one of claims 1 through 28 wherein R_1 is $-X-Y-R_4$.

33. The method of claim 32 wherein X is C_{2-4} alkylene, and Y is $-S(O)_2-$ or $-N(R_8)-Q-$.

34. The method of claim 33 wherein $-X-Y-R_4$ is selected from the group consisting of 2-(propylsulfonyl)ethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 4-methylsulfonylaminobutyl, and 2-(acetylamino)-2-methylpropyl.

35. The method of any one of claims 1 through 28 wherein R_1 is $-X-R_5$.

36. The method of claim 35 wherein $-X-R_5$ is 4-[(morpholin-4-ylcarbonyl)amino]butyl.

37. The method of any one of claims 1 through 36 wherein R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

38. The method of claim 37 wherein R_A and R_B are each methyl.

39. The method of any one of claims 1 through 36 wherein R_A and R_B taken together form a fused benzene ring wherein the benzene ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group.

40. The method of claim 39 wherein the fused benzene ring is substituted by one R group selected from the group consisting of hydroxy and bromo.

41. The method of claim 39 wherein the fused benzene ring is substituted by one R_3 group wherein R_3 is methoxy, phenoxy, or benzyloxy.

42. The method of any one of claims 1 through 36 wherein R_A and R_B taken together form a fused pyridine ring wherein the fused pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group; and wherein the fused pyridine ring is



, wherein the highlighted bond indicates the position where the ring is fused.

43. The method of claim 39 or 42 wherein the R is hydroxy or bromo, and R_3 is methoxy, phenoxy, or benzyloxy.

44. The method of claim 42 wherein the fused pyridine ring is substituted by one R group selected from the group consisting of hydroxy and bromo.

45. The method of claim 42 wherein the fused pyridine ring is substituted by one R_3 group wherein R_3 is methoxy, phenoxy, or benzyloxy.

46. The method of any one of claims 1 through 7 or any one of claims 17 through 26 as dependent on any one of claims 1 through 7 wherein R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is R_{2a}, wherein:

R_{A1} and R_{B1} are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_{A1} and R_{B1} taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R_a group, or substituted by one R_{3a} group, or substituted by one R_a group and one R_{3a} group;

or R_{A1} and R_{B1} taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R_a groups;

R_a is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
trifluoromethyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_{1a} is selected from the group consisting of:
$-R_{4a}$,
$-X-R_{4a}$,
$-X-Y_a-R_{4a}$,
$-X-Y_a-X-Y_a-R_{4a}$,
$-X-R_{5a}$,
$-N(R_1')-Q-R_{4a}$,
$-N(R_1')-X_1-Y_1-R_{4a}$, and
$-N(R_1')-X_1-R_{5b}$;

R_{2a} is selected from the group consisting of:
$-R_{4a}$,
$-X-R_{4a}$,

-X-Y_a-R_{4a}, and

-X-R_{5a};

R_{3a} is selected from the group consisting of:

-Z-R_{4a},

-Z-X-R_{4a},

-Z-X-Y_a-R_{4a},

-Z-X-Y_a-X-Y_a-R_{4a}, and

-Z-X-R_{5a};

Y_a is selected from the group consisting of:

-O-,

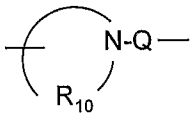
-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

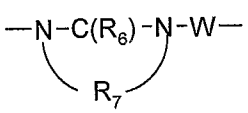
-$N(R_8)$-Q-,

-O-$C(R_6)$-$N(R_8)$-,

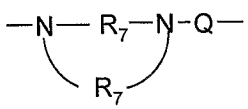
-$C(R_6)$-$N(OR_9)$-,



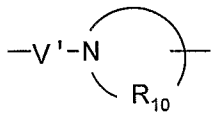
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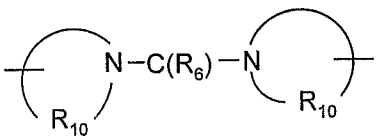
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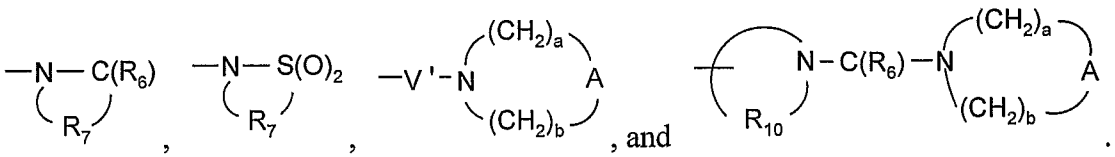


;

R_{4a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, trifluoromethoxy, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, and (dialkylamino)alkyleneoxy; and

R_{5a} is selected from the group consisting of:



47. The method of claim 46 wherein R_{2a} is $-R_{4a}$.

48. The method of claim 47 wherein R_{2a} is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, ethoxymethyl, and hydroxymethyl.

49. The method of any one of claims 8 through 16 or any one of claims 17 through 26 as dependent on any one of claims 8 through 16 wherein R_A is R_{A1}, R_B is R_{B1}, R_1 is R_{1a}, and R_2 is hydrogen, wherein:

R_{A1} and R_{B1} are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_{A1} and R_{B1} taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R_a group, or substituted by one R_{3a} group, or substituted by one R_a group and one R_{3a} group;

or R_{A1} and R_{B1} taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R_a groups;

R_a is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
trifluoromethyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_{1a} is selected from the group consisting of:

$-R_{4a}$,
$-X-R_{4a}$,
$-X-Y_a-R_{4a}$,
$-X-Y_a-X-Y_a-R_{4a}$,
$-X-R_{5a}$,
$-N(R_1')-Q-R_{4a}$,
$-N(R_1')-X_1-Y_1-R_{4a}$, and
$-N(R_1')-X_1-R_{5b}$;

R_{3a} is selected from the group consisting of:

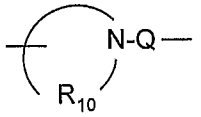
$-Z-R_{4a}$,
$-Z-X-R_{4a}$,
$-Z-X-Y_a-R_{4a}$,
$-Z-X-Y_a-X-Y_a-R_{4a}$, and
$-Z-X-R_{5a}$;

Y_a is selected from the group consisting of:

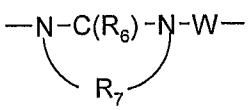
$-O-$,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-N(R_8)-Q-$,

-O-C(R_6)-N(R_8)-,

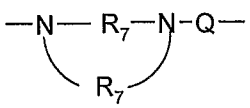
-C(R_6)-N(OR_9)-,



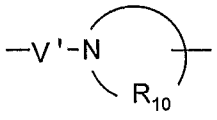
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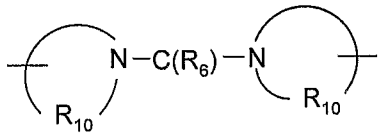
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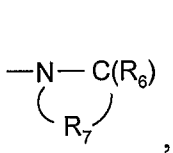
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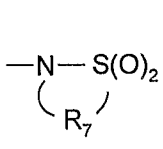
;

R_{4a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, trifluoromethyl, trifluoromethoxy, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, and (dialkylamino)alkyleneoxy; and

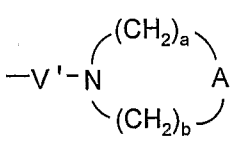
R_{5a} is selected from the group consisting of:



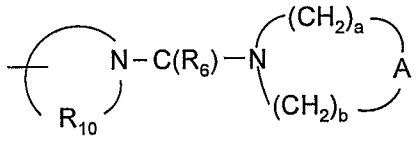
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,



, and



.

50. The method of any one of claims 46 through 49 wherein R_{1a} is -R_{4a} or -X-R_{4a}.

51. The method of claim 50 wherein -R_{4a} is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, and (1-hydroxycyclobutyl)methyl, and -X-R_{4a} is 2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl.

52. The method of claim 51 wherein -R_{4a} is 2-methylpropyl.

53. The method of any one of claims 46 through 49 wherein R_{1a} is -X-Y_a-R_{4a}.

54. The method of claim 53 wherein X is C_{2-4} alkylene, and Y_a is -$S(O)_2$- or -$N(R_8)$-Q-.

55. The method of claim 54 wherein -X-Y_a-R_{4a} is selected from the group consisting of 2-(propylsulfonyl)ethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 4-methylsulfonylaminobutyl, and 2-(acetylamino)-2-methylpropyl.

56. The method of any one of claims 46 through 49 wherein R_{1a} is -X-R_{5a}.

57. The method of claim 56 wherein -X-R_{5a} is 4-[(morpholin-4-ylcarbonyl)amino]butyl.

58. The method of any one of claims 46 through 57 wherein R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and -$N(R_9)_2$.

59. The method of claim 58 wherein R_{A1} and R_{B1} are each methyl.

60. The method of any one of claims 46 through 57 wherein R_{A1} and R_{B1} taken together form a fused benzene ring wherein the benzene ring is unsubstituted or substituted by one R_a group, or substituted by one R_{3a} group, or substituted by one R_a group and one R_{3a} group.

61. The method of claim 60 wherein the fused benzene ring is substituted by one R_a group selected from the group consisting of hydroxy and bromo.

62. The method of claim 60 wherein the fused benzene ring is substituted by one R_{3a} group wherein R_{3a} is methoxy, phenoxy, or benzyloxy.

63. The method of claim 39 or 60 wherein the fused benzene ring is unsubstituted.

64. The method of any one of claims 46 through 57 wherein R_{A1} and R_{B1} taken together form a fused pyridine ring wherein the fused pyridine ring is unsubstituted or substituted by one R_a group, or substituted by one R_{3a} group, or substituted by one R_a group and one R_{3a} group; and wherein the fused pyridine ring is



, wherein the highlighted bond indicates the position where the ring is fused.

65. The method of claim 60 or 64 wherein the R_a is hydroxy or bromo, and R_{3a} is methoxy, phenoxy, or benzyloxy.

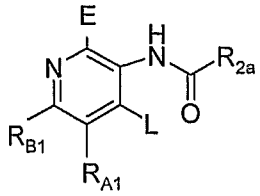
66. The method of claim 64 wherein the fused pyridine ring is substituted by one R_a group selected from the group consisting of hydroxy and bromo.

67. The method of claim 64 wherein the fused pyridine ring is substituted by one R_{3a} group wherein R_{3a} is methoxy, phenoxy, or benzyloxy.

68. The method of claim 42 or 64 wherein the fused pyridine ring is unsubstituted.

69. The method of any one of claims 1 through 7 or any one of claims 17 through 45 as dependent on any one of claims 1 through 7 wherein reacting the compound of Formula IV with an amine of the formula R_1NH_2 is carried out neat and at an elevated temperature.

70. The method of any one of claims 46 through 48 and 50 through 68 as dependent on any one of claims 1 through 7 wherein Formula IV is the Formula IV_a:

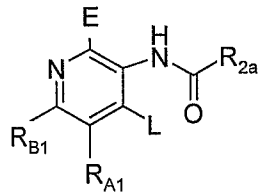


IV_a,

and wherein reacting the compound of Formula IV_a with an amine of the formula $R_{1a}NH_2$ is carried out neat and at an elevated temperature.

71. The method of any one of claims 1 through 7 or any one of claims 17 through 45 as dependent on any one of claims 1 through 7 wherein reacting the compound of Formula IV with an amine of the formula R_1NH_2 is carried out in a solvent and at an elevated temperature.

72. The method of any one of claims 46 through 48 and 50 through 68 as dependent on any one of claims 1 through 7 wherein Formula IV is the Formula IV_a:



IV_a,

and wherein reacting the compound of Formula IV_a with an amine of the formula $R_{1a}NH_2$ is carried out in a solvent and at an elevated temperature.

73. The method of claim 71 or claim 72 wherein the solvent is selected from the group consisting of methanol, ethanol, trifluoroethanol, isopropanol, *tert*-butanol, water, acetonitrile, 1-methyl-2-pyrrolidinone, and toluene.

74. The method of claim 73 wherein the solvent is selected from the group consisting of trifluoroethanol, isopropanol, and *tert*-butanol.

75. The method of any one of claims 69 through 74 wherein the elevated temperature is not lower than 80 °C.

76. The method of any one of claims 69 through 75 wherein the elevated temperature is not lower than 110 °C.

77. The method of any one of claims 69 through 76 wherein the elevated temperature is not higher than 180 °C.

78. The method of any one of claims 69 through 77 wherein the elevated temperature is not higher than 165 °C.

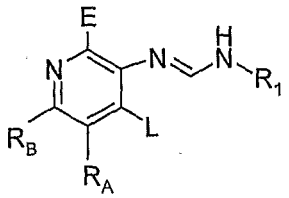
79. The method of any one of claims 8 through 12, claim 16 as dependent on claim 11 or claim 12, or any one of claims 17 through 26 and 29 through 45 as dependent on any one of claims 8 through 12 wherein reacting the compound of Formula VIII with an amine of the formula R_1NH_2 is carried out neat.

80. The method of any one of claims 8 through 12, claim 16 as dependent on claim 11 or claim 12, or any one of claims 17 through 26 and 29 through 45 as dependent on any one of claims 8 through 12 wherein reacting the compound of Formula VIII with an amine of the formula R_1NH_2 is carried out in solvent.

81. The method of claim 80 wherein the solvent is selected from the group consisting of methanol, ethanol, trifluoroethanol, isopropanol, *tert*-butanol, water, acetonitrile, 1-methyl-2-pyrrolidinone, toluene, and tetrahydrofuran.

82. The method of claim 81 wherein the solvent is selected from the group consisting of trifluoroethanol, isopropanol, *tert*-butanol, and acetonitrile.

83. A compound of the Formula XI:

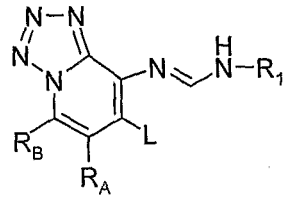


XI

wherein:

E is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, phenoxy, -O-S(O)$_2$-R', and -N(Bn)$_2$, wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro, and Bn is selected from the group consisting of benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and 2-furanylmethyl; or

E is joined with the adjacent pyridine nitrogen atom of Formula XI to form the fused tetrazolo ring in Formula XIII:



XIII;

L is selected from the group consisting of fluoro, chloro, bromo, iodo, phenoxy, and -O-S(O)$_2$-R', wherein R' is selected from the group consisting of alkyl, haloalkyl, and aryl optionally substituted by alkyl, halo, or nitro;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

or R_A and R_B taken together form a fused benzene ring or a fused pyridine ring wherein the benzene ring or pyridine ring is unsubstituted or substituted by one R group, or substituted by one R_3 group, or substituted by one R group and one R_3 group;

or R_A and R_B taken together form a fused 5 to 7 membered saturated ring optionally containing one nitrogen atom, wherein the fused ring is unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$,
$-X-Y-X-Y-R_4$,
$-X-R_5$,
$-N(R_1')-Q-R_4$,
$-N(R_1')-X_1-Y_1-R_4$, and
$-N(R_1')-X_1-R_{5b}$;

R_3 is selected from the group consisting of:

$-Z-R_4$,
$-Z-X-R_4$,
$-Z-X-Y-R_4$,
$-Z-X-Y-X-Y-R_4$, and
$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X_1 is C_{2-20} alkylene;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-$N(R_8)$-Q-,

-O-$C(R_6)$-$N(R_8)$-,

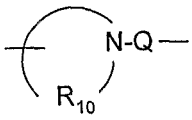
-$C(R_6)$-$N(OR_9)$-,

-O-$N(R_8)$-Q-,

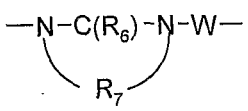
-O-N=$C(R_4)$-,

-C(=N-O-R_8)-,

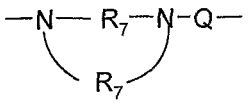
-CH(-N(-O-R_8)-Q-R_4)-,



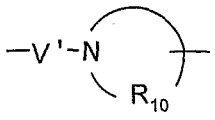
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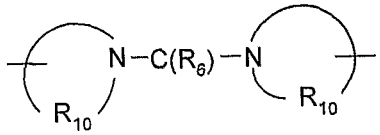
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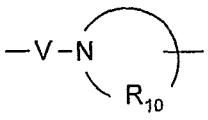
,



, and



;

Y_1 is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, and 

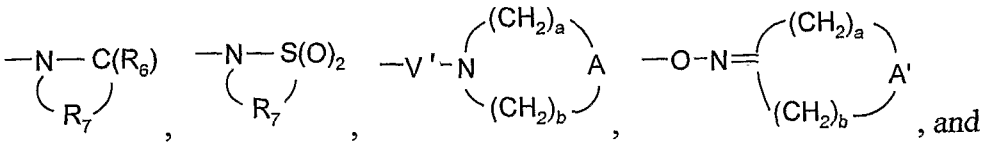
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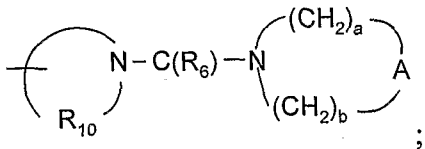
Z is a bond or -O-;

R_1' is selected from the group consisting of hydrogen, C_{1-20} alkyl, hydroxy-C_{2-20} alkylenyl, and alkoxy-C_{2-20} alkylenyl;

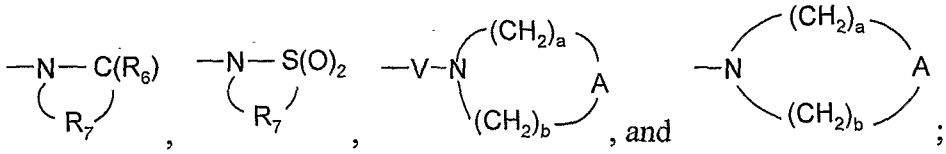
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


, and


;

R_{5b} is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, and –$N(R_4)$-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -$N(-Q-R_4)$-, and -CH_2-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

V' is selected from the group consisting of -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

84. The compound or salt of claim 83 wherein R_1 is -R_4 or -X-R_4.

85. The compound or salt of claim 84 wherein -R_4 is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,2-dimethyl-4-oxopentyl, and (1-hydroxycyclobutyl)methyl, and -X-R_4 is 2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl.

86. The compound or salt of claim 85 wherein -R_4 is 2-methylpropyl.

87. The compound or salt of claim 83 wherein R_1 is -X-Y-R_4.

88. The compound or salt of claim 87 wherein X is C_{2-4} alkylene, and Y is -S(O)$_2$- or -N(R_8)-Q-.

89. The compound or salt of claim 88 wherein -X-Y-R_4 is selected from the group consisting of 2-(propylsulfonyl)ethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 4-methylsulfonylaminobutyl, and 2-(acetylamino)-2-methylpropyl.

90. The compound or salt of claim 83 wherein R_1 is -X-R_5.

91. The compound or salt of claim 90 wherein -X-R_5 is 4-[(morpholin-4-ylcarbonyl)amino]butyl.

92. The compound or salt of any one of claims 83 through 91 wherein R_A and R_B taken together form a fused benzene ring wherein the benzene ring is unsubstituted.

93. The compound or salt of any one of claims 83 through 91 wherein R_A and R_B taken together form a fused pyridine ring wherein the fused pyridine ring is unsubstituted, and wherein the fused pyridine ring is



, wherein the highlighted bond indicates the position where the ring is fused.