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(54) **Title:** CHIRAL FUSED [1,2]IMIDAZO[4,5-*c*] RING COMPOUNDS

(57) **Abstract:** Fused [1,2]imidazo[4,5-*c*] ring compounds (*e.g.*, imidazo[4,5-c]quinolines, 6,7,8,9-tetrahydroimidazo[4,5-c]quinolines, imidazo[4,5-c]naphthyridines, and 6,7,8,9-tetrahydroimidazo[4,5-c]naphthyridines) with a -CH(-X_1-R_1)-group in the fused ring at the 1-position of the imidazo ring, pharmaceutical compositions containing the compounds, intermediates, methods of making the compounds, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases, are disclosed.

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CHIRAL FUSED [1,2]IMIDAZO[4,5-*c*] RING COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application Serial No. 60/640,614, filed December 30, 2004, and U.S. Provisional Application Serial No. 60/697,257, filed July 7, 2005, both of which are incorporated herein by reference.

BACKGROUND

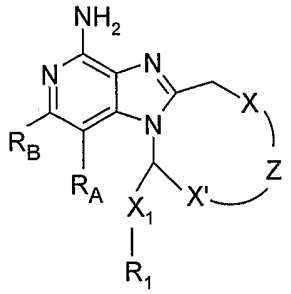
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*] pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

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.

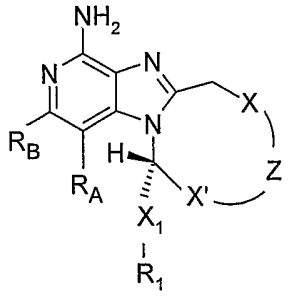
SUMMARY

It has now been found that certain fused [1,2]imidazo[4,5-c] ring compounds modulate cytokine biosynthesis. Such compounds are of the following Formula I:

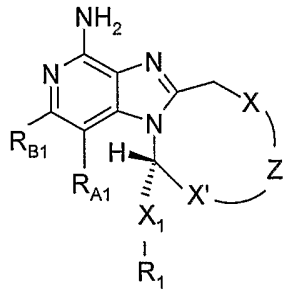


I

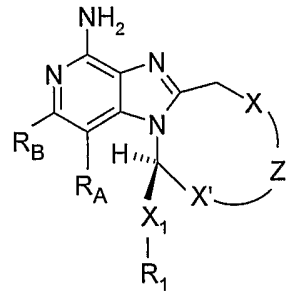
and, more particularly, compounds of the following Formulas II, IIa, II-1, and II-1a:



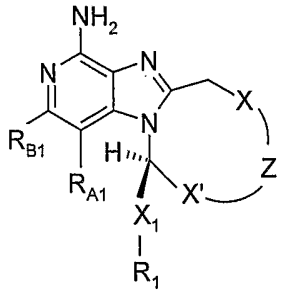
II



IIa



II-1



II-1a

wherein: X, X', X_1, Z, R_1, R_A, R_B, R_{A1}, and R_{B1} are as defined below.

The compounds of Formulas I, II, IIa, II-1, and II-1a are useful, for example, as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce or inhibit the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of a compound of Formulas I, II, IIa, II-1, or II-1a and methods of inducing cytokine biosynthesis in an animal, treating a viral infection and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula II or Formula IIa to the animal.

In addition, methods of synthesizing compounds of Formulas I, II, IIa, II-1, and II-1a and intermediates useful in the synthesis of these compounds are provided.

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

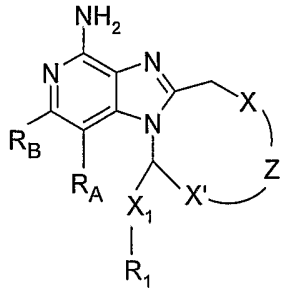
The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

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

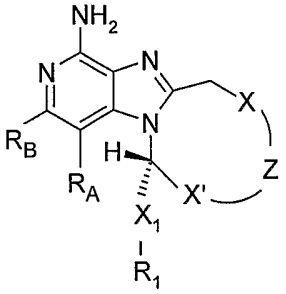
only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formulas I, II, IIa, II-1, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, and VII-1:



I



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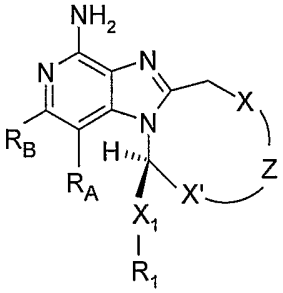
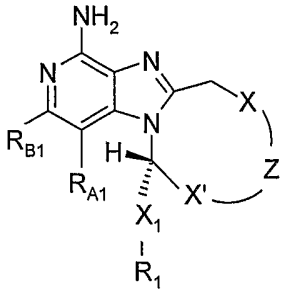
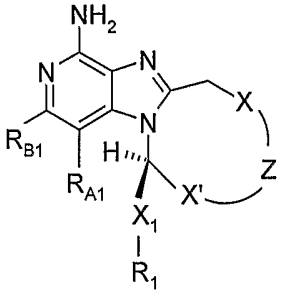


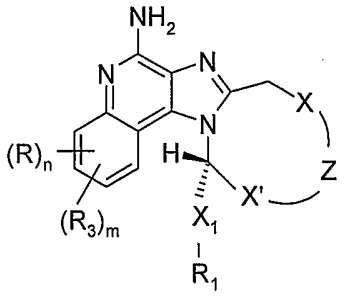
II-1



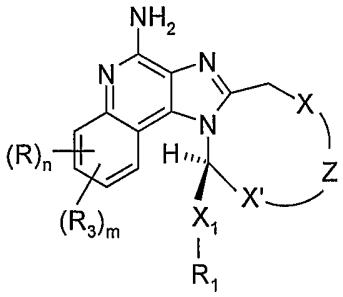
IIa



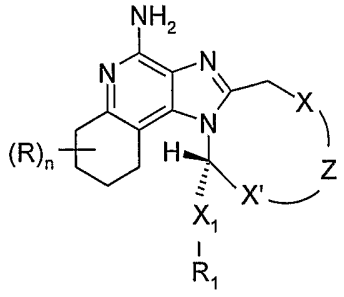
II-1a



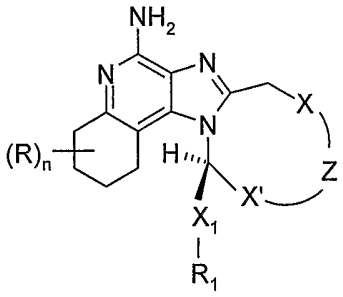
III



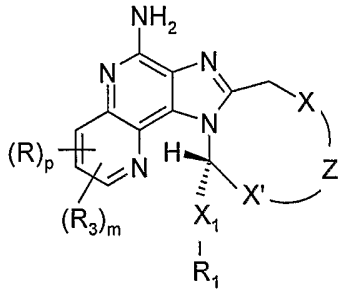
III-1



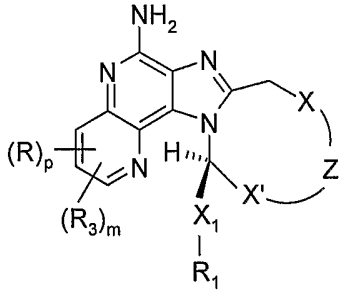
IV



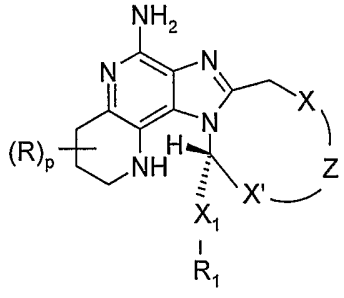
IV-1



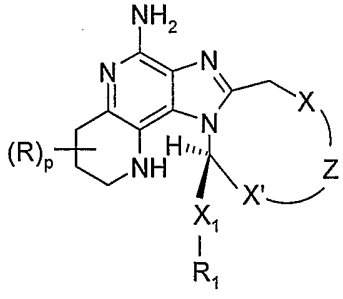
V



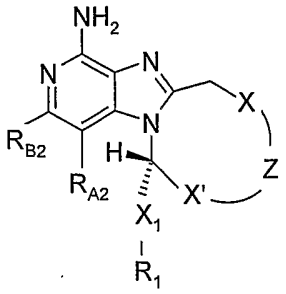
V-1



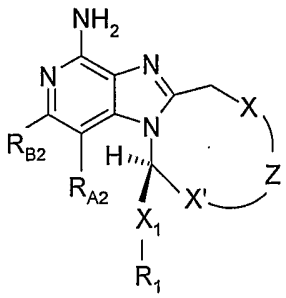
VI



VI-1

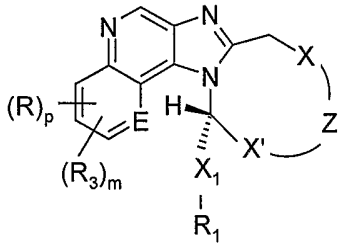


VII

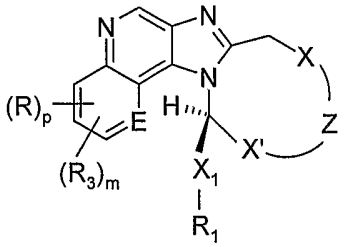


VII-1

as well as intermediates of the following Formulas X and X-1:



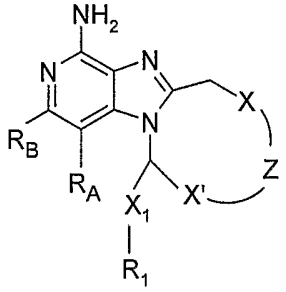
X



X-1

wherein: X, X', X_1, Z, R, R_1, R_3, R_A, R_B, R_{A1}, R_{B1}, R_{A2}, R_{B2}, E, m, n, and p are as defined below.

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



I

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

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 when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and 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' is a non-interfering substituent;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

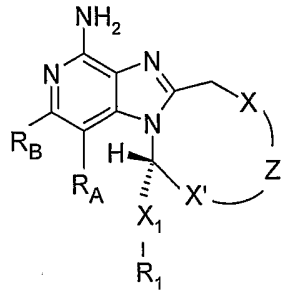
R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula I, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

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



II

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino,

arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

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 when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and 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' is a non-interfering substituent;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

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

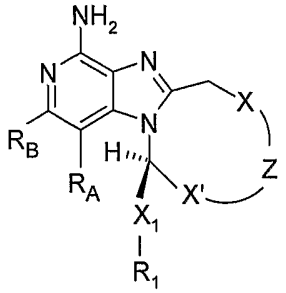
or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula II, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

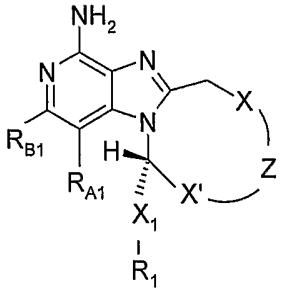
In other embodiments, the present invention provides a compound of Formula II-1:



II-1

wherein X, X', Z, R_1, X_1, R_A, and R_B are as defined in any one of the embodiments of Formula II above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula IIa:



IIa

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

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 when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and 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_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

R_3 is selected from the group consisting of:

$-Y''-R_4$,

$-Z'-R_4$,

$-Z'-X''-R_4$,

$-Z'-X''-Y'-R_4$,

$-Z'-X''-Y'-X''-Y'-R_4$, 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;

Y' is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

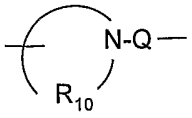
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

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

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

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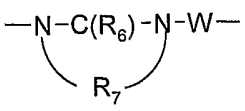
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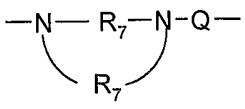
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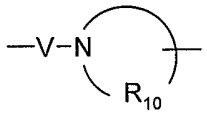
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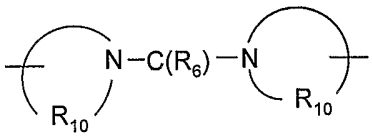
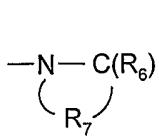

;

Y" is -O-C(R_6)-;

Z' is a bond or -O-;

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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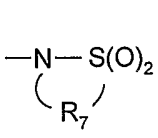
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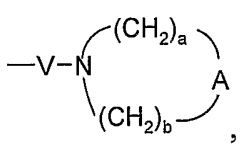
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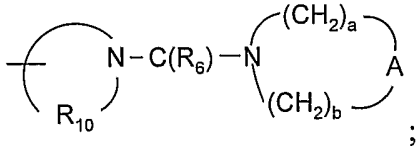

;

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, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

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 $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

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

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.

In another embodiment of Formula IIa, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and

R_3 is selected from the group consisting of:

-Z'-R_4,

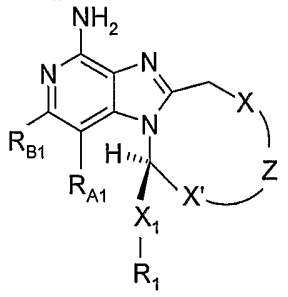
-Z'-X"-R_4,

-Z'-X"-Y'-R_4,

-Z'-X"-Y'-X"-Y'-R_4, and

-Z'-X"-R_5.

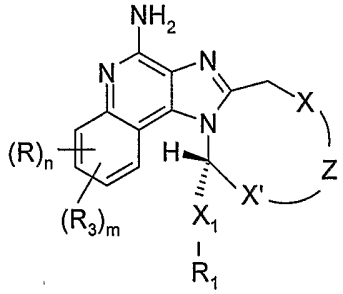
In other embodiments, there is provided a compound of Formula II-1a:



II-1a

wherein X, X', Z, R_1, X_1, R_{A1}, and R_{B1} are as defined in any one of the embodiments of Formula IIa above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula III:



III

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

R_3 is selected from the group consisting of:

$-Y''-R_4$,

$-Z'-R_4$,

$-Z'-X''-R_4$,

$-Z'-X''-Y'-R_4$,

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

$-Z'-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

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;

Y' is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

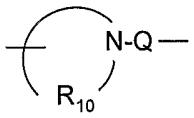
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

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

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

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



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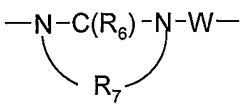

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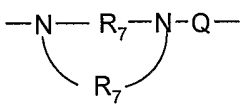

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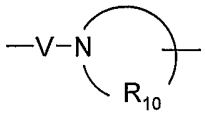
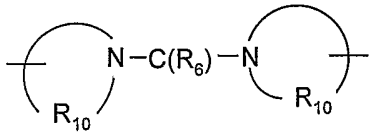


, and



;

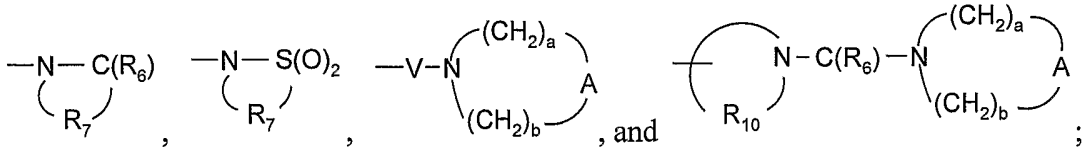
Y'' is $-O-C(R_6)-$;

Z' is a bond or -O-;

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_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, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

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 $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

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

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.

In another embodiment of Formula III, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and

R_3 is selected from the group consisting of:

-Z'-R_4,

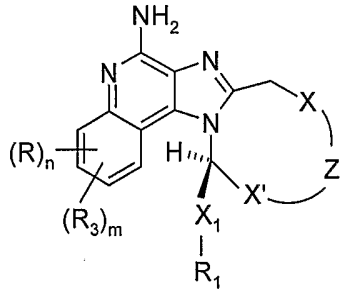
-Z'-X"-R_4,

-Z'-X"-Y'-R_4,

-Z'-X"-Y'-X"-Y'-R_4, and

-Z'-X"-R_5.

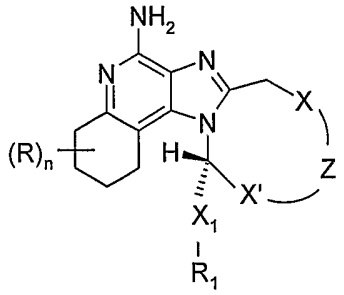
In other embodiments, there is provided a compound of Formula III-1:



III-1

wherein X, X', Z, R_1, X_1, R, R_3, m, and n are as defined in any one of the embodiments Formula III above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula IV:



IV

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino,

arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

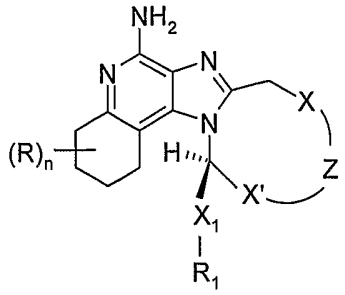
R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula IV, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

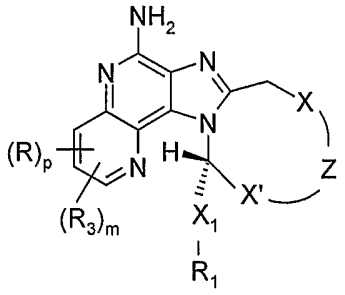
In other embodiments, there is provided a compound of Formula IV-1:



IV-1

wherein X, X', Z, R_1, X_1, R, and n are as defined in any one of the embodiments of Formula IV above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula V:



V

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

p is an integer from 0 to 3;

R_2 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; alkylthio; alkanoyl; alkanoyloxy;

alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

R_3 is selected from the group consisting of:

$-Y''-R_4$,

$-Z'-R_4$,

$-Z'-X''-R_4$,

$-Z'-X''-Y'-R_4$,

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

$-Z'-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

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;

Y' is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

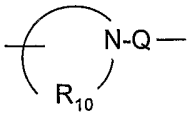
-O-C(O)-O-,

-N(R_8)-Q-,

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

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

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



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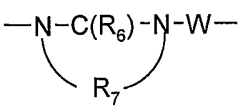

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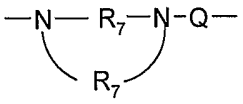

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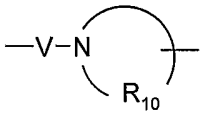

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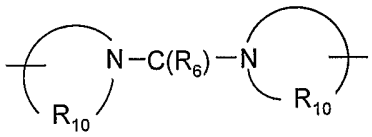


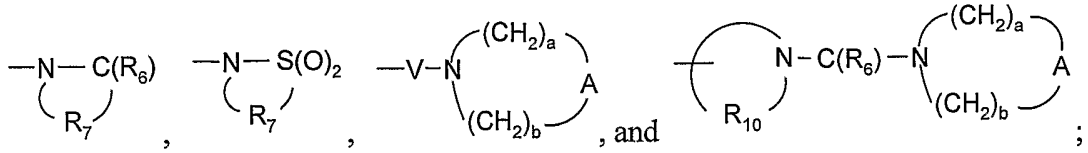
;

Y" is -O-C(R_6)-;

Z' is a bond or -O-;

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_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, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

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 $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

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

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.

In another embodiment of Formula V, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of

alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and

R_3 is selected from the group consisting of:

-Z'-R_4,

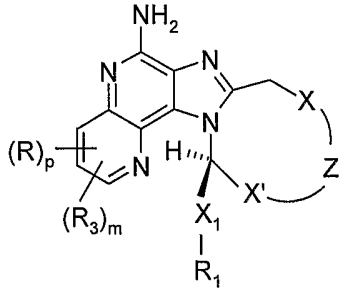
-Z'-X"-R_4,

-Z'-X"-Y'-R_4,

-Z'-X"-Y'-X"-Y'-R_4, and

-Z'-X"-R_5.

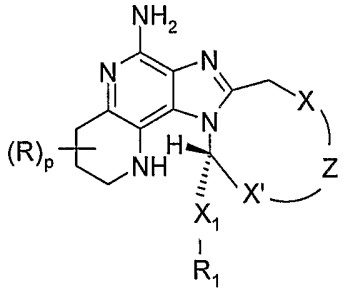
In other embodiments, there is provided a compound of Formula V-1:



V-1

wherein X, X', Z, R_1, X_1, R, R_3, m, and p are as defined in any one of the embodiments of Formula V above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula VI:



VI

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

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

p is an integer from 0 to 3;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,
$-S(O)_2-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-N(R_8)-$,
$-C(R_6)-N(R_8)-C(R_6)-$,
$-C(R_6)-N(R_8)-S(O)_2-$, and
$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

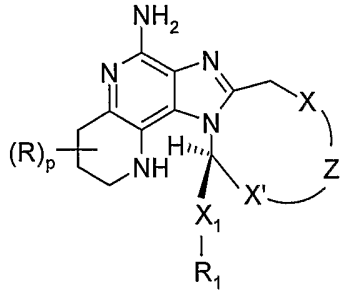
R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula VI, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

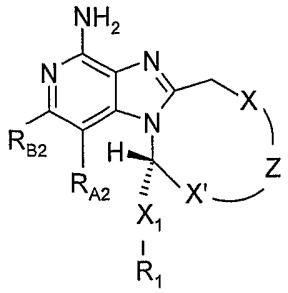
In other embodiments, there is provided a compound of Formula VI-1:



VI-1

wherein X, X', Z, R_1, X_1, R, and p are as defined in any one of the embodiments of Formula VI above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula VII:



VII

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino,

arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

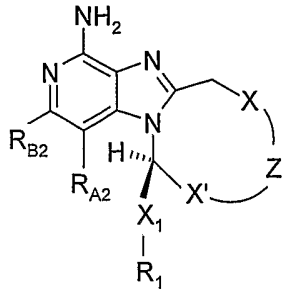
R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula VII, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

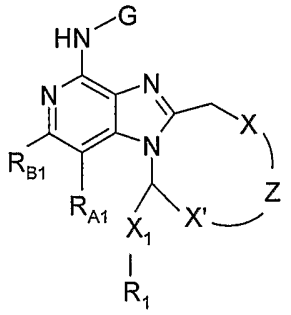
In other embodiments, there is provided a compound of Formula VII-1:



VII-1

wherein X, X', Z, R_1, X_1, R_{A2}, and R_{B2} are as defined in any one of the embodiments of Formula VII above; or a pharmaceutically acceptable salt thereof.

For certain embodiments, the present invention provides a compound (which is a prodrug) of the Formula VIII:



VIII

wherein:

G is selected from the group consisting of:

-C(O)-R",

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R",

-C(O)-N(R"')R",

-C(=NY_2)-R",

-CH(OH)-C(O)-OY_2,

-CH(OC_{1-4} alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R" and R"' are independently selected from the group consisting of C_{1-10} alkyl,

C_{3-7} cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R''' can also be hydrogen;

α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y_2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

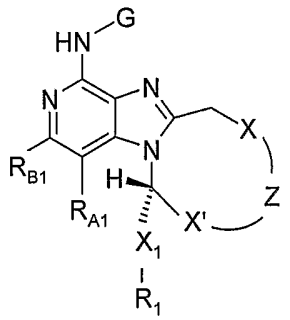
Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl; and

X, X', Z, R_1, X_1, R_{A1}, and R_{B1} are as defined in any one of the embodiments of Formula IIa above;

or a pharmaceutically acceptable salt thereof.

For certain embodiments, there is provided a compound (which is a prodrug) of the Formula IX:

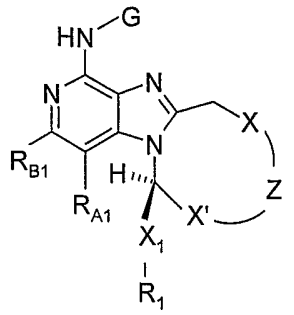


IX

wherein G, X, X', Z, R_1, X_1, R_{A1}, and R_{B1} are as defined in any one of the embodiments Formula VIII above;

or a pharmaceutically acceptable salt thereof.

For certain embodiments, there is provided a compound (which is a prodrug) of the Formula IX-1:

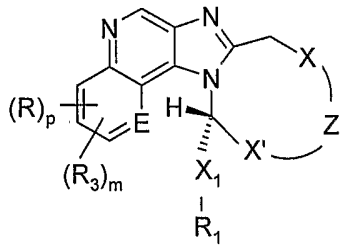


IX-1

wherein G, X, X', Z, R_1, X_1, R_{A1}, and R_{B1} are as defined in any one of the embodiments of Formula VIII above;

or a pharmaceutically acceptable salt thereof.

In one embodiment, there is provided an intermediate compound of the following Formula X:



X

wherein:

E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and p is 0 or 1, and with the further proviso that when E is CR and m is 1, p is 0;

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-$N(R_9)_2$;

p is an integer from 0 to 3;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

R_3 is selected from the group consisting of:

$-Y''-R_4$,

$-Z'-R_4$,

$-Z'-X''-R_4$,

$-Z'-X''-Y'-R_4$,

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

$-Z'-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

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;

Y' is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

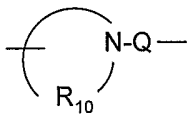
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

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

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

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



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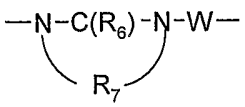

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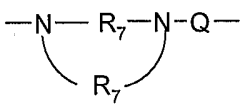

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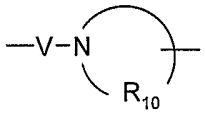
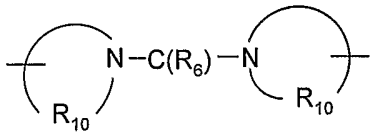


, and



;

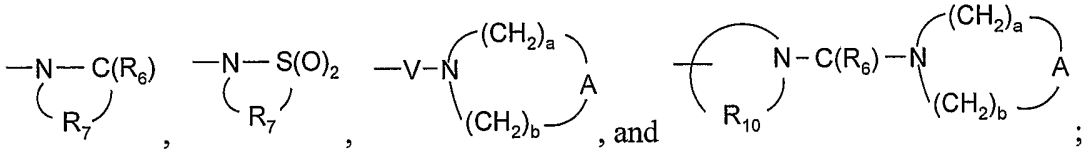
Y'' is $-O-C(R_6)-$;

Z' is a bond or -O-;

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_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, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

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 $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

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

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.

In another embodiment of Formula X, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and

R_3 is selected from the group consisting of:

-Z'-R_4,

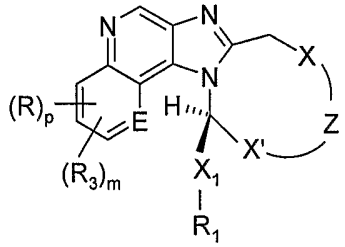
-Z'-X"-R_4,

-Z'-X"-Y'-R_4,

-Z'-X"-Y'-X"-Y'-R_4, and

-Z'-X"-R_5.

In other embodiments, intermediate compounds of Formula X-1:



X-1

are provided wherein X, X', Z, R_1, X_1, E, R, R_3, m, and p are as defined in any one of the embodiments of Formula X above;

or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. For certain embodiments, R'

is a non-interfering substituent. Illustrative non-interfering R' groups include those described above for R and R_3.

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, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms 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. In some embodiments, the term "heteroaryl" includes one ring that contains 2-5 carbon atoms, 1-3 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. In some embodiments, the term "heterocyclyl" includes one or two rings that contain 2-9 carbon atoms, 1-3 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" are the divalent forms 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 aryl ring" includes fused carbocyclic aromatic rings or ring systems. Examples of fused aryl rings include benzo, naphtho, fluoreno, and indeno.

The term "fused heteroaryl ring" includes the fused forms of 5 or 6 membered aromatic rings that contain one heteroatom selected from S and N. Examples of fused heteroaryl rings include pyrido and thieno.

The term "fused 5 to 7 membered saturated ring" includes rings which are fully saturated except for the bond where the ring is fused. In one example, the ring is a cyclohexene ring. In other examples wherein one heteroatom (N or S) is present, the ring is tetrahydropyrido or dihydrothieno.

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, for the formula $-N(R_9)_2$ each R_9 group is independently selected. In another example, when a Y and a Y' group are both present and both contain an R_8 group, each R_8 group is independently selected. In a further example, when more than one Y' group is present (i.e., R_3 contains two Y' groups) and each Y' group contains one or more R_7 groups, then each Y' group is independently selected, and each R_7 group is independently selected.

The invention is inclusive of the compounds described herein (including intermediates) in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In particular, the invention specifically includes mixtures of the compound with its enantiomer in any ratio as well as the racemic mixture. Ratios of the compound to its enantiomer include, for example, 50:50 or higher, 90:10 or higher, 95:5 or higher, 99:1 or higher, 99.9:0.1 or higher, or 100:0. 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).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by vaious mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series,

and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For any of the compounds presented herein, each one of the following variables (e.g., X, X', X_1, Z, R, R_1, R_3, R_A, R_B, R_{A1}, R_{B1}, R_{A2}, R_{B2}, E, m, n, and p and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R is halogen or hydroxy.

For certain embodiments, R is $-N(R_9)_2$.

For certain embodiments, R is (cyclopropylmethyl)amino.

For certain embodiments, R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino. For certain of these embodiments, when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may further be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, and haloarylenyl; and when R_1 is

heterocyclyl, then the one or more substituents may further be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl.

For certain embodiments, R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo.

For certain embodiments, R_1 is selected from the group consisting of alkyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, and alkoxy.

For certain embodiments, R_1 is selected from the group consisting of alkyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein alkyl is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen and hydroxy.

For certain embodiments, R_1 is C_{1-3} alkyl optionally substituted by hydroxy or one or more fluorine atoms.

For certain embodiments, R_1 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, halogen, hydroxy, aryl, heteroaryl, and heterocyclyl; and wherein when R_1 is heteroaryl, then the one or more substituents may also be independently selected from the group consisting of haloarylenyl, alkoxyarylenyl, alkylarylenyl, and arylalkylenyl; and wherein when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl and aminocarbonyl.

For certain embodiments, R_1 is heterocyclyl which is selected from the group consisting of morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, thiazolidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, 1,3-dioxolanyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxyC_{1-4} alkyl, hydroxy, aminocarbonyl, arylC_{1-4} alkylenyl, and 5 to 7 membered heterocyclyl containing one or two heteroatoms.

For certain embodiments, R_1 is tetrahydro-2*H*-pyran-4-yl or 2,2,-dimethyl-1,3-dioxolanyl.

For certain embodiments, R_1 is heteroaryl which is selected from the group consisting of pyridyl, pyrazolyl, oxazolyl, and triazolyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxyC_{1-4} alkyl, haloC_{1-4} alkyl, aryl, aryl substituted by fluoro, chloro, methyl, or methoxy, arylC_{1-4} alkylenyl, and heteroaryl.

For certain embodiments, R_1 is pyrazolyl, oxazolyl, or triazolyl; wherein triazolyl is unsubstituted or substitued by methyl, ethyl, propyl, butyl, hydoxymethyl, hydroxyethyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, pyridin-2-yl, or pyridin-3-yl; and wherein pyrazolyl and oxazolyl are each unsubstituted or substituted by methyl, ethyl, *n*-butyl, 2-methylpropyl, trifluoromethyl, phenyl, or benzyl.

For certain embodiments, R_1 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkenyl, and C_{1-4} alkynyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, and aryl.

For certain embodiments, R_1 is methyl or isopropyl.

For certain embodiments, R_1 is 1-fluoro-1-methylethyl.

For certain embodiments, R_1 is 1-hydroxy-1-methylethyl.

For certain embodiments, R_1 is 1-hydroxyethyl.

For certain embodiments, R_1 is phenyl, benzyl, pyridinyl, or pyridinylmethyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, and alkoxy.

For certain embodiments, R_1 is phenyl, benzyl, pyridinyl, or pyridinylmethyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of fluoro, chloro, and hydroxy.

For certain embodiments, R_1 is phenyl, benzyl, pyridinyl, or pyridinylmethyl.

For certain embodiments, R_1 is benzyl.

For certain embodiments, R_1 is aryl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl, and hydroxyC_{1-4} alkyl.

For certain embodiments, R_1 is phenyl.

For certain embodiments, R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy.

For certain embodiments, R_2 is alkyl.

For certain embodiments, R_2 is methyl.

For certain embodiments, R_3 is selected from the group consisting of -Y"-R_4, -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 embodiments, 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 embodiments, R_3 is selected from the group consisting of benzyloxy which is unsubstituted or substituted by halogen or haloalkyl, 3-pyrrolylpropoxy, 2-(4-methoxyphenyl)-2-oxoethoxy, aryl, and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, hydroxy, hydroxyalkyl, alkoxy, halogen, dialkylamino,

alkylcarbonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, and heterocyclylcarbonyl. In certain of these embodiments, heterocyclylcarbonyl is pyrrolidinylcarbonyl or morpholinylcarbonyl.

For certain embodiments, R_3 is phenyl substituted by pyrrolidinylcarbonyl or morpholinylcarbonyl.

For certain embodiments, R_3 is benzyloxy.

For certain embodiments, R_3 is -Z'-R_4, and R_4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl; wherein alkyl and alkenyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, alkoxy, cyano, and aryl; wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, halogen, cyano, and dialkylamino; and wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

For certain embodiments, R_3 is -Z'-R_4, Z' is -O-, and R_4 is alkynyl.

For certain embodiments, R_3 is -Z'-R_4, Z' is a bond, and R_4 is heterocyclyl which is selected from the group consisting of pyrrolidinyl, piperidinyl, oxazolidinyl, morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

For certain embodiments, R_3 is is 2-oxopyrrolidin-1-yl, morpholin-1-yl, or 2-oxo-1,3-oxazolidin-3-yl.

For certain embodiments, R_3 is -Z'-X"-R_4.

For certain embodiments, R_3 is -Z'-X"-R_4, wherein X" is C_{1-3} alkylene or C_{1-3} alkenylene, and R_4 is heterocyclyl or heteroaryl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo, and wherein heteroaryl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, cyano, and dialkylamino.

For certain embodiments, R_3 is -Z'-X"-R_4; wherein X" is C_{1-3} alkylene or C_{1-3} alkenylene, and R_4 is heterocyclyl which is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

For certain embodiments, R_3 is -Z'-X"-R_4; wherein X" is C_{1-3} alkylene or C_{1-3} alkenylene, and R_4 is heteroaryl which is selected from the group consisting of thiazolyl, imidazolyl, isoxazolyl, and pyridinyl each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, cyano, and dialkylamino.

For certain embodiments, R_3 is -Z'-X"-R_4; wherein X" is C_{1-3} alkylene, and R_4 is pyridin-3-yl, 1-methyl-1*H*-imidazol-2-yl, or 1,3-thiazol-4-yl.

For certain embodiments, R_3 is -Z'-X"-Y'-R_4.

For certain embodiments, R_3 is -Z'-X"-Y'-R_4; wherein X" is selected from the group consisting of C_{1-3} alkylene, C_{1-3} alkenylene, piperidin-1,4-diyl, and phenylene; Y' is selected from the group consisting of -$C(R_6)$-, -$C(R_6)$-O-, -$C(R_6)$-$N(R_8)$-, -$N(R_8)$-Q-, and -$S(O)_2$- wherein Q is selected from the group consisting of a bond, -C(O)-, -$S(O)_2$-, -and $C(R_6)$-$N(R_8)$-; R_6 is selected from the group consisting of =O and =S; and R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl; and R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and heterocyclyl; wherein alkyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, alkoxy, and aryl; wherein aryl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, halogen, cyano, dialkylamino, and alkoxy; and wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl and oxo.

For certain embodiments, R_3 is -Z'-X"-Y'-R_4; wherein X" is selected from the group consisting of C_{1-3} alkylene, C_{1-3} alkenylene, piperidin-1,4-diyl, and phenylene; Y' is -$N(R_8)$-Q- wherein R_8 is hydrogen, and Q is -$S(O)_2$-, -C(O)-, or -C(O)-NH-; and R_4 is C_{1-3} alkyl or pyridyl.

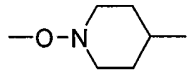
For certain embodiments, R_3 is -Z'-X"-Y'-R_4; wherein X" is selected from the group consisting of C_{1-3} alkylene, C_{1-3} alkenylene, piperidin-1,4-diyl, and phenylene, Y' is -NH-$S(O)_2$-, and R_4 is methyl; or Y' is -NH-C(O)-, and R_4 is 3-pyridyl; or Y' is -C(O)-NH-, and R_4 is hydrogen or C_{1-3} alkyl.

For certain embodiments, R_3 is -Z'-X"-Y'-R_4; wherein Z' is a bond, X" is C_{2-3} alkylene, Y' is -NH-$S(O)_2$-, -NH-C(O)-, or -NH-C(O)-NH-, and R_4 is C_{1-3} alkyl.

For certain embodiments, R_3 is -Z'-X"-Y'-R_4; wherein Z' is -O-, X" is C_{2-3} alkylene, Y' is -$S(O)_2$- or -NH-$S(O)_2$-, and R_4 is C_{1-3} alkyl.

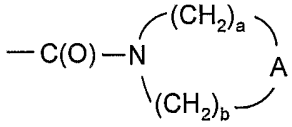
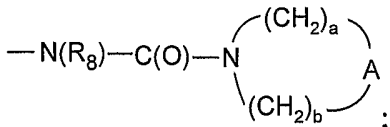
For certain embodiments, R_3 is -Z'-X"-Y'-R_4; wherein X" is selected from the group consisting of C_{1-3} alkylene, C_{1-3} alkenylene, piperidin-1,4-diyl, and phenylene, Y' is -C(O)-, and R_4 is heterocyclyl.

For certain embodiments, R_3 is -Z'-X"-Y'-R_4; wherein X" is selected from the group consisting of C_{1-3} alkylene, C_{1-3} alkenylene, piperidin-1,4-diyl, and phenylene, Y' is -C(O)-, and R_4 is is selected from the group consisting of pyrrolidinyl, piperidinyl, thiazolidinyl, aziridinyl, azepanyl, diazepanyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and piperazinyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl and oxo.

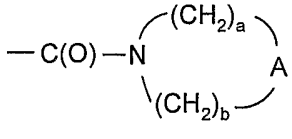
For certain embodiments, R_3 is -Z'-X"-Y'-R_4; wherein -Z'-X"- is  , Y' is -C(O)-, -C(O)-NH-, or -$S(O)_2$-, and R_4 is methyl, ethyl, or 1-methylethyl.

For certain embodiments, R_3 is -Z'-X"-R_5.

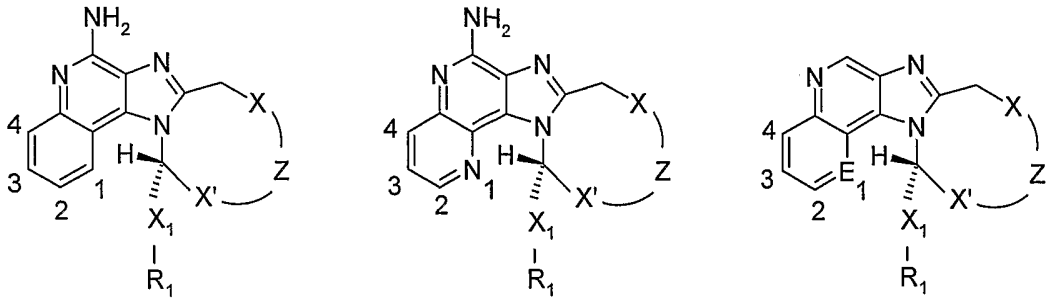
For certain embodiments, R_3 is -Z'-X"-R_5; wherein X" is selected from the group consisting of C_{1-3} alkylene and phenylene, and R_5 is selected from the group consisting of:

 and  ; wherein A is -O-, -S-, or -SO_2-; R_8 is hydrogen or C_{1-4} alkyl; and a and b are each independently an integer of 1 to 3.

For certain embodiments, R_3 is -Z'-X"-R_5; wherein X" is phenylene, and R_5 is

 ; wherein A is -O-, and a and b are each 2.

For certain embodiments, R_3 is at the 3-position with the positions numbered as follows:



For certain embodiments, 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 embodiments, R_4 is alkyl, arylalkylenyl, aryl, or heteroaryl.

For certain embodiments, R_4 is hydrogen or C_{1-3} alkyl.

For certain embodiments, R_4 is C_{1-3} alkyl or pyridyl.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and heterocyclyl; wherein alkyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, alkoxy, and aryl; wherein aryl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, halogen, cyano, dialkylamino, and alkoxy; and wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl and oxo.

For certain embodiments, R_4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl; wherein alkyl and alkenyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, alkoxy, cyano, and aryl; wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents independently selected from the

group consisting of alkyl, alkoxy, hydroxyalkyl, halogen, cyano, and dialkylamino; and wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

For certain embodiments, R_4 is heteroaryl which is selected from the group consisting of thiazolyl, imidazolyl, isoxazolyl, and pyridinyl each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, cyano, and dialkylamino.

For certain embodiments, R_4 is heterocyclyl.

For certain embodiments, R_4 is is selected from the group consisting of pyrrolidinyl, piperidinyl, thiazolidinyl, aziridinyl, azepanyl, diazepanyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and piperazinyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl and oxo.

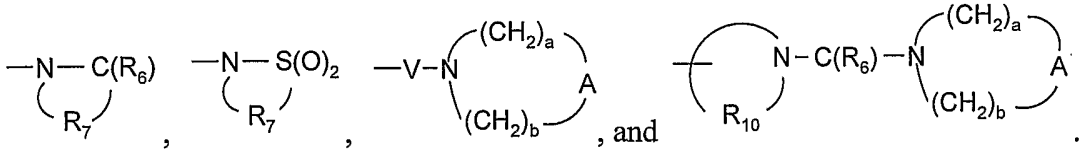
For certain embodiments, R_4 is heterocyclyl which is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

For certain embodiments, R_4 heterocyclyl or heteroaryl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo, and wherein heteroaryl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, cyano, and dialkylamino.

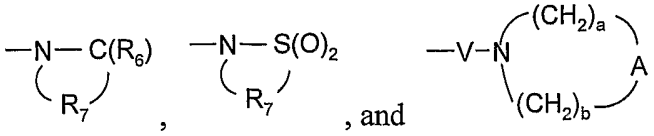
For certain embodiments, R_4 is heterocyclyl which is selected from the group consisting of pyrrolidinyl, piperidinyl, oxazolidinyl, morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

For certain embodiments, R_4 is alkynyl.

For certain embodiments, R_5 is selected from the group consisting of:

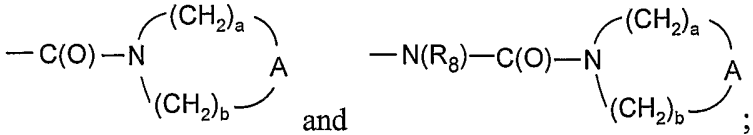


For certain embodiments, R_5 is selected from the group consisting of:

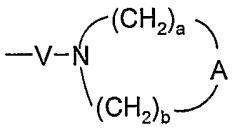


, and wherein V is -N(R_8)-C(O)-.

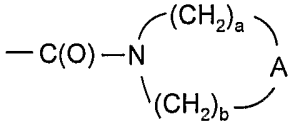
For certain embodiments, R_5 is selected from the group consisting of:



and ; wherein A is -O-, -S-, or -SO_2-; R_8 is hydrogen or C_{1-4} alkyl; and a and b are each independently an integer of 1 to 3.

For certain embodiments, R_5 is 

wherein V is -C(O)-.

For certain embodiments, R_5 is 

; wherein A is -O-, and a and b are each 2.

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_6 is =O.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_7 is propylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl

For certain embodiments, R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_8 is hydrogen or methyl.

For certain embodiments, R_8 is hydrogen.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_9 is alkyl.

For certain embodiments, R_9 is hydrogen.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_{10} is pentylene.

For certain 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 when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

For certain 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 embodiments, R_A and R_B form a fused aryl ring or heteroaryl ring.

For certain embodiments, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom.

For certain embodiments, 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 when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group; or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

For certain embodiments, R_{A1} and R_{B1} form a benzo ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments, R_{A1} and R_{B1} form a benzo ring which is unsubstituted.

For certain embodiments, R_{A1} and R_{B1} form a pyrido ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments, R_{A1} and R_{B1} form a pyrido ring which is unsubstituted.

For certain embodiments, the pyrido ring is  wherein the highlighted bond indicates the position where the ring is fused.

For certain embodiments, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted.

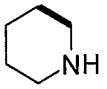
For certain embodiments, R_{A1} and R_{B1} form a fused cyclohexene ring that is unsubstituted or substituted by one, two, three, or four R groups.

For certain embodiments, R_{A1} and R_{B1} form a fused cyclohexene ring that is unsubstituted.

For certain embodiments, R_{A1} and R_{B1} form a tetrahydropyrido ring that is unsubstituted or substituted on one or more ring carbon atoms by one, two, or three R groups.

For certain embodiments, R_{A1} and R_{B1} form a tetrahydropyrido ring that is unsubstituted.

For certain embodiments, the tetrahydropyrido ring is

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

For certain embodiments, R_{A2} and R_{B2} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R_{A2} and R_{B2} are each methyl.

For certain embodiments, A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$.

For certain embodiments, A is -O-, -S-, or $-SO_2-$.

For certain embodiments, A is -O-.

For certain embodiments, E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and p is 0 or 1, and with the further proviso that when E is CR and m is 1, p is 0. For certain embodiments, E is CH. For certain embodiments, E is N. For certain embodiments, E is CR. For certain embodiments, E is CR_3.

For certain embodiments, Q is selected from the group consisting of a bond,

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

For certain embodiments, Q is selected from the group consisting of a bond, $-C(O)-$, $-S(O)_2-$, -and $C(R_6)-N(R_8)-$.

For certain embodiments, Q is $-S(O)_2-$, $-C(O)-$, or $-C(O)-NH-$.

For certain embodiments, Q is $-C(R_6)-$.

For certain embodiments, Q is $-S(O)_2-$.

For certain embodiments, Q is $-C(R_6)-N(R_8)-W-$.

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

For certain embodiments, V is $-N(R_8)-C(O)-$.

For certain embodiments, V is $-C(O)-$.

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

For certain embodiments, W is a bond.

For certain embodiments, X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms.

For certain embodiments, X is a bond.

For certain embodiments, X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms.

For certain embodiments, X' contributes one ring carbon atom.

For certain embodiments, X' is C_{1-2} alkylene.

For certain embodiments, X' is methylene.

For certain embodiments, X' contributes two ring carbon atoms.

In each of the above embodiments of X and X', X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3.

For certain embodiments, X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group.

For certain embodiments, X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups.

For certain embodiments, X_1 is a bond or alkylene.

For certain embodiments, X_1 is C_{1-4} alkylene.

For certain embodiments, X_1 is $-CH_2-$.

For certain embodiments, X_1 is a bond.

For certain embodiments, X_1 is C_{1-4} alkylene substituted by a hydroxy or methoxy group.

For certain embodiments, X_1 is C_{2-3} alkylene interrupted by one -O- group.

For certain embodiments, X_1 is C_{2-3} alkenylene or C_{2-3} alkynylene.

For certain embodiments, 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 embodiments, X" is C_{1-3} alkylene or C_{1-3} alkenylene.

For certain embodiments, X" is alkylene.

For certain embodiments, X" is selected from the group consisting of C_{1-3} alkylene, C_{1-3} alkenylene, piperidin-1,4-diyl, and phenylene.

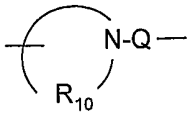
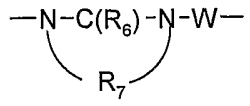
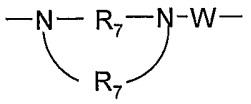
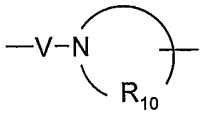
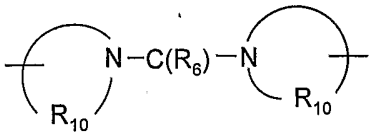
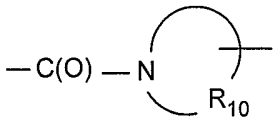
For certain embodiments, X" is selected from the group consisting of C_{1-3} alkylene and phenylene.

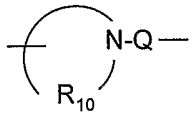
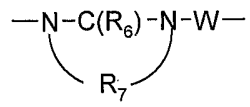
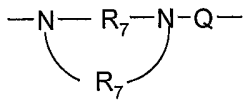
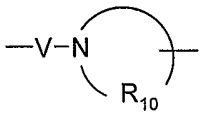
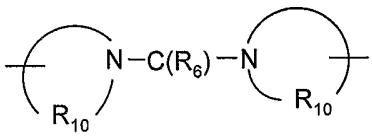
For certain embodiments, Y is selected from the group consisting of a bond, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(R_8)-C(R_6)-$, $-C(R_6)-N(R_8)-S(O)_2-$, and $-C(R_6)-O-$.

For certain embodiments, Y is selected from the group consisting of -C(O)-, $-S(O)_2-$, and -C(O)-NH-.

For certain embodiments, Y is $-S(O)_2-$.

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

-O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,  ,  ,  ,  ,  , and  .

For certain embodiments, Y' is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,  ,  ,  ,  , and  .

For certain embodiments, Z is selected from the group consisting of -O- and -N(-Y-R_2)-.

For certain preferred embodiments, Z is -O-.

For certain embodiments, Z is -N(-Y-R_2)-.

For certain embodiments, Z' is a bond or -O-.

For certain embodiments, Z' is a bond.

For certain embodiments, Z' is -O-.

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

For certain embodiments, a and b are each independently an integer of 1 to 3.

For certain embodiments, a and b are each 2.

For certain embodiments, m is 0 or 1.

For certain embodiments, m is 0.

For certain embodiments, m is 1.

For certain embodiments, n is an integer from 0 to 4.

For certain embodiments, n is 0 or 1.

For certain embodiments, n is 0.

For certain embodiments, n is 1.

For certain embodiments, n is 2.

For certain embodiments, n is 3 or 4.

For certain embodiments, p is an integer from 0 to 3.

For certain embodiments, p is 0 or 1.

For certain embodiments, p is 0.

For certain embodiments, p is 1.

For certain embodiments, m is 1 and n is 0.

For certain embodiments, m is 0 and n is 0.

For certain embodiments, m is 1 and p is 0.

For certain embodiments, m is 0 and p is 0.

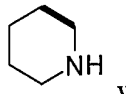
In some embodiments, particularly embodiments of Formulas I, II, or II-1, the one or more R' groups are one or more R groups, or one R_3 group, or one R_3 group and one R group; wherein R and R_3 are as defined in Formula IIa or are any one of the embodiments of R and R_3 defined above.

In some embodiments, particularly embodiments of Formula I, R_A and R_B form a benzo ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group. For certain embodiments, R_A and R_B form a benzo ring which is unsubstituted.

In some embodiments, particularly embodiments of Formula I, R_A and R_B form a pyrido ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group. For certain embodiments, R_A and R_B form a pyrido ring which is unsubstituted. For certain embodiments, the pyrido ring is  wherein the highlighted bond indicates the position where the ring is fused.

In some embodiments, particularly embodiments of Formula I, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted. For certain embodiments, R_A and R_B form a fused cyclohexene ring that is unsubstituted or substituted by one, two, three, or four R groups. For certain embodiments, R_A and R_B form a fused

cyclohexene ring that is unsubstituted. For certain embodiments, R_A and R_B form a tetrahydropyrido ring that is unsubstituted or substituted on one or more ring carbon atoms by one, two, or three R groups. For certain embodiments, R_A and R_B form a tetrahydropyrido ring that is unsubstituted. For certain embodiments, the tetrahydropyrido ring is



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

In some embodiments, particularly embodiments of Formula I, 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 embodiments, R_A and R_B are each methyl.

In some embodiments, particularly embodiments of Formulas VII or VII-1, R_{A2} and R_{B2} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. In certain of these embodiments, R_{A2} and R_{B2} are each methyl.

In some embodiments, particularly embodiments of Formulas III, III-1, IV, or IV-1, n is an integer from 0 to 4, with the proviso that in Formulas III and III-1 when m is 1, then n is 0 or 1. In certain of these embodiments, n is 0.

In some embodiments, particularly embodiments of Formulas V, V-1, VI or VI-1, p is an integer from 0 to 3, with the proviso that in Formulas V and V-1 when m is 1, then p is 0 or 1. In certain of these embodiments, p is 0.

In some embodiments, particularly embodiments of Formulas III or III-1, n is an integer from 0 to 4 and m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1. In certain of these embodiments, n and m are 0.

In some embodiments, particularly embodiments of Formulas V or V-1, p is an integer from 0 to 3, and m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1. In certain of these embodiments, p and m are 0.

In some embodiments, particularly embodiments of Formulas X, or X-1, E is CH or N, p is 0, and m is 0 or 1. In certain of these embodiments, p and m are 0.

In some embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, R_3 is selected from the group consisting of benzyloxy which is unsubstituted or substituted by halogen or haloalkyl, 3-pyrrolylpropoxy, 2-(4-methoxyphenyl)-2-oxoethoxy, aryl, and heteroaryl, wherein aryl and heteroaryl are

unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, hydroxy, hydroxyalkyl, alkoxy, halogen, dialkylamino, alkylcarbonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, and heterocyclylcarbonyl.

For certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, R_3 is phenyl substituted by pyrrolidinylcarbonyl or morpholinylcarbonyl.

In certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, R_3 is benzyloxy. For certain of these embodiments of Formulas III and III-1, n is 0. For certain of these embodiments of Formulas V, V-1, X, and X-1, p is 0

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VIII, IX, IX-1, X, or X-1, R is halogen or hydroxy. For certain of these embodiments of Formulas III and III-1, m is 0, and n is 1. For certain of these embodiments of Formulas V, V-1, X, and X-1, m is 0 and p is 1.

In certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VIII, IX, IX-1, X, or X-1, R is $-N(R_9)_2$. For certain of these embodiments of Formulas III and III-1, m is 0, and n is 1. For certain of these embodiments of Formulas V and V-1, m is 0, and p is 1. For certain of these embodiments, R is (cyclopropylmethyl)amino.

In certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, wherein R_3 is benzyloxy, R is halogen or hydroxy. For certain of these embodiments of Formulas III and III-1, m is 1 and n is 1.

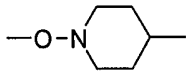
For certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, R_3 is $-Z'-R_4$. For certain of these embodiments, R_4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein alkyl and alkenyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, alkoxy, cyano, and aryl; wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, halogen, cyano, and dialkylamino; and wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from alkyl

and oxo. For certain of these embodiments, Z' is -O-, and R_4 is alkynyl. For certain of these embodiments, R_4 is propynyl. Alternatively, for certain of these embodiments, Z' is a bond and R_4 is heterocyclyl which is selected from the group consisting of pyrrolidinyl, piperidinyl, oxazolidinyl, morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo. For certain of these embodiments, -Z'-R_4 is 2-oxopyrrolidin-1-yl, morpholin-1-yl, or 2-oxo-1,3-oxazolidin-3-yl.

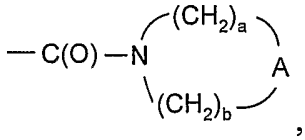
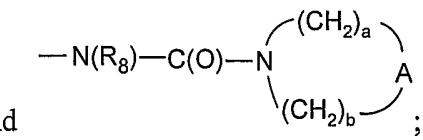
For certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, X-1, embodiments of Formula III or III-1 wherein n is 0, or embodiments of Formula V or V-1 wherein p is 0, R_3 is -Z'-X"-R_4. For certain of these embodiments, X" is C_{1-3} alkylene or C_{1-3} alkenylene, and R_4 is heterocyclyl or heteroaryl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo, and wherein heteroaryl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, cyano, and dialkylamino. For certain of these embodiments, R_4 is heterocyclyl which is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo. Alternatively, for certain of these embodiments, R_4 is heteroaryl which is selected from the group consisting of thiazolyl, imidazolyl, isoxazolyl, and pyridinyl each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, cyano, and dialkylamino. For certain of these embodiments, X" is C_{1-3} alkylene, and R_4 is pyridin-3-yl, 1-methyl-1*H*-imidazol-2-yl, or 1,3-thiazol-4-yl.

For certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, X-1, embodiments of Formula III or III-1 wherein n is 0, or embodiments of Formula V or V-1 wherein p is 0, R_3 is -Z'-X"-Y'-R_4. For certain of these embodiments, X" is selected from the group consisting of C_{1-3} alkylene, C_{1-3} alkenylene, piperidin-1,4-diyl, and phenylene, Y' is selected from the group consisting of -$C(R_6)$-, -$C(R_6)$-O-, -$C(R_6)$-N(R_8)-, -N(R_8)-Q-, and -$S(O)_2$- wherein Q is selected from the group consisting of a bond, -C(O)-, -$S(O)_2$-, -and $C(R_6)$-N(R_8)-, R_6 is selected from the group consisting of =O and =S, and R_8 is selected from the group consisting of hydrogen,

C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl; and R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and heterocyclyl; wherein alkyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, alkoxy, and aryl; wherein aryl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, halogen, cyano, dialkylamino, and alkoxy; and wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl and oxo. For certain of these embodiments, Y' is -N(R_8)-Q- wherein R_8 is hydrogen, Q is -S(O)$_2$-, -C(O)-, or -C(O)-NH-, and R_4 is C_{1-3} alkyl or pyridyl. For certain of these embodiments, Y' is -NH-S(O)$_2$- and R_4 is methyl, or Y' is -NH-C(O)- and R_4 is 3-pyridyl, or Y' is -C(O)-NH- and R_4 is hydrogen or C_{1-3} alkyl. For certain of these embodiments, Z' is a bond, X" is C_{2-3} alkylene, Y' is -NH-S(O)$_2$-, -NH-C(O)-, or -NH-C(O)-NH-, and R_4 is C_{1-3} alkyl. Alternatively, for certain of these embodiments, Z' is -O-, X" is C_{2-3} alkylene, Y' is -S(O)$_2$- or -NH-S(O)$_2$-, and R_4 is C_{1-3} alkyl. Alternatively, for certain of these embodiments, Y' is -C(O)- and R_4 is heterocyclyl. For certain of these embodiments, heterocyclyl is selected from the group consisting of pyrrolidinyl, piperidinyl, thiazolidinyl, aziridinyl, azepanyl, diazepanyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and piperazinyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl and oxo.

Alternatively, for certain of these embodiments, -Z'-X"- is  , Y' is -C(O)-, -C(O)-NH-, or -S(O)$_2$-, and R_4 is methyl, ethyl, or 1-methylethyl.

For certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, X-1, embodiments of Formula III or III-1 wherein n is 0, or embodiments of Formula V or V-1 wherein p is 0, R_3 is -Z'-X"-R_5. For certain of these embodiments, X" is selected from the group consisting of C_{1-3} alkylene and phenylene, and R_5 is selected from the group consisting of:

 , and  ; wherein A is

-O-, -S-, or -SO_2-; R_8 is hydrogen or C_{1-4} alkyl; and a and b are each independently an integer of 1 to 3. For certain of these embodiments, A is -O-, and a and b are each 2.

For certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, X-1, embodiments of Formula III or III-1 wherein n is 0, or embodiments of Formula V or V-1 wherein p is 0, R_3 is -Y"-R_4. For certain of these embodiments, R_4 is heterocyclyl. For certain of these embodiments, R_4 is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo. For certain of these embodiments, R_4 is pyrrolidin-1-yl or morpholin-4-yl.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, Z is -N(-Y-R_2)-.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments (except where Z is -N(-Y-R_2)-), Z is -O-.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments (except where Z is -O-), Y is selected from the group consisting of -C(O)-, -$S(O)_2$-, and -C(O)-NH-. In certain of these embodiments, Y is -$S(O)_2$- and R_2 is methyl.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, R_1 is selected from the group consisting of alkyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, and alkoxy. In certain of these embodiments, R_1 is selected from the group consisting of alkyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein alkyl is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen and hydroxy. In certain of these embodiments, R_1 is C_{1-3} alkyl optionally substituted by hydroxy or one or more fluorine atoms. In certain of these embodiments, R_1 is phenyl, benzyl, pyridinyl, or pyridinylmethyl, each of which is

unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, and alkoxy. In certain of these embodiments, R_1 is phenyl, benzyl, pyridinyl, or pyridinylmethyl.

For certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments which include the following definition of R_1, R_1 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, halogen, hydroxy, aryl, heteroaryl, and heterocyclyl; and wherein when R_1 is heteroaryl, then the one or more substituents may also be independently selected from the group consisting of haloarylenyl, alkoxyarylenyl, alkylarylenyl, and arylalkylenyl; and wherein when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl and aminocarbonyl. For certain of these embodiments, R_1 is heterocyclyl which is selected from the group consisting of morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, thiazolidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, 1,3-dioxolanyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxyC_{1-4} alkyl, hydroxy, aminocarbonyl, arylC_{1-4} alkylenyl, and 5 to 7 membered heterocyclyl containing one or two heteroatoms. Alternatively, for certain of these embodiments, R_1 is heteroaryl which is selected from the group consisting of pyridyl, pyrazolyl, oxazolyl, and triazolyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxyC_{1-4} alkyl, haloC_{1-4} alkyl, aryl, aryl substituted by fluoro, chloro, methyl, or methoxy, arylC_{1-4} alkylenyl, and heteroaryl.

For certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments which include the following definition of R_1, R_1 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkenyl, and C_{1-4} alkynyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, and aryl.

For certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments which include the following definition of R_1, R_1 is aryl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl, and hydroxyC_{1-4} alkyl.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, X_1 is a bond or alkylene. For certain of these embodiments, X is a bond. Alternatively, for certain of these embodiments, X_1 is $-CH_2-$.

For certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments which includes the following definition of X_1, X_1 is C_{1-4} alkylene substituted by a hydroxy or methoxy group.

For certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments which includes the following definition of X_1, X_1 is C_{2-3} alkylene interrupted by one -O- group.

For certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments which includes the following definition of X_1, X_1 is C_{2-3} alkenylene or C_{2-3} alkynylene.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, X is a bond.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, X' contributes one ring carbon atom.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, X' is C_{1-2} alkylene. In certain of these embodiments, X' is methylene.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments (except where X' contributes one ring carbon atom or X' is methylene), X' contributes two ring carbon atoms.

For certain embodiments of the compounds of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, or VII-1, or any one of the above embodiments of these Formulas, the $-NH_2$ group can be replaced by an -NH-G group, as shown in the compounds of Formulas VIII, IX, and IX-1, to form prodrugs. In such embodiments, G is selected from the group consisting of: -C(O)-R", α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R", -C(O)-N(R'")R", -C(=NY_2)-R", -CH(OH)-C(O)-OY_2, -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, and -$CH(CH_3)Y_1$. For certain embodiments, G is selected from the group consisting of -C(O)-R", α-aminoacyl, α-aminoacyl-α-aminoacyl, and -C(O)-O-R". Preferably, R" and R'" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and $-S(O)_2-NH_2$, with the proviso that R'" can also be hydrogen. Preferably, α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids. Preferably, Y_2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl. Preferably, Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl. Preferably, Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl.

In some embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, or IX-1 or any one of the above embodiments and a pharmaceutically acceptable carrier.

In some embodiments, the present invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas to the animal.

In some embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas to the animal.

In some embodiments, the present invention provides a method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas to the animal.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. 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)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds 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*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. 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.

Compounds of the invention can be prepared according to Reaction Scheme I, wherein R, R_1, X_1, X, and X' are as defined above; Hal is chloro, bromo, or iodo; E is carbon (imidazoquinolines) or nitrogen (imidazonaphthyridines); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring); and P is a hydroxy

protecting group. In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XV is treated with an amino alcohol of Formula XVI to provide a compound of Formula XVII. Several amino alcohols of Formula XVI are commercially available, such as (*S*)-1-amino-2-propanol, L-valinol, (*S*)-2-phenylglycinol, and (*S*)-2-amino-3-phenyl-1-propanol. Others can be prepared by known synthetic methods; for example, see the methods described in Williams, L. et al., *Tetrahedron*, *52*, pp. 11673-11694, (1996) and Genevois-Borella, A. et al., *Tetrahedron Lett.*, *31*, pp. 4879-4882 (1990) for the preparation of amino alcohols wherein R_1 includes a hydroxy substituent. A hydroxy substituent on R_1 can readily be converted to a halogen substituent using a variety of known methods; for example, a hydroxy substituent can be converted to a fluoro substituent using (diethylaminosulfur) trifluoride in a suitable solvent such as dichloromethane at a sub-ambient temperature such as –78 °C.

The reaction in step (1) is conveniently carried out by adding the amino alcohol of Formula XVI to a solution of 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XV in a suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at an elevated temperature such as, for example, the reflux temperature of the solvent. Many compounds of Formula XV are known or can be prepared using known synthetic methods, see for example, U.S. Patent Nos. 4,689,338; 5,175,296; 5,367,076; 5,389,640; 6,194,425; and U.S. Patent Publication Application No. US 2004/0147543 and the documents cited therein.

In step (2) of Reaction Scheme I, the hydroxy group of a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XVII is protected using conventional techniques to provide a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XVIII. A number of suitable protecting groups can be used; in particular, protecting groups that would survive the reduction in step (3) are preferred. Suitable protecting groups include but are not limited to silyl groups such as the *tert*-butyl dimethylsilyl group. The reaction is conveniently carried out by treating the hydroxy-substituted compound of Formula XVII with *tert*-butyldimethylsilyl chloride in the presence of a base such as triethylamine and catalytic 4-(dimethylamino)pyridine (DMAP). The reaction can be carried out in a suitable solvent such as dichloromethane or

pyridine at an elevated temperature such as the reflux temperature of the solvent or a temperature in the range of 50 °C to 70 °C.

Compounds of Formula XVIII may also be prepared in step (1) of Reaction Scheme I if the hydroxy group on a compound of Formula XVI is protected before the reaction. The protection of the hydroxy group on a compound of Formula XVI can be carried out as described above in step (2).

In step (3) of Reaction Scheme I, a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XVIII is reduced to provide a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XIX. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, isopropanol, ethyl acetate, or acetonitrile. The reaction can be carried out at ambient temperature.

In step (4) of Reaction Scheme I, a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XIX is reacted with a carboxylic acid equivalent, which is selected such that it will provide the desired -X-Hal substituent in a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XX. Suitable carboxylic acid equivalents include ortho esters, acid halides, imidates, and imidate salts.

When the carboxylic acid equivalent is an imidate of formula Hal-CH_2-X-C(=NH)-O-alkyl or a salt thereof, the reaction is conveniently carried out by combining a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XIX with the imidate in a suitable solvent such 1,2-dichloroethane, chloroform, or propyl acetate. The reaction can be carried out at an elevated temperature such as a temperature not lower than 55 °C and not higher than 85 °C or at the reflux temperature of the solvent. Some imidates of formula Hal-CH_2-X-C(=NH)-O-alkyl are known; others can be prepared by known methods. Ethyl chloroacetimidate hydrochloride, which can be used to provide a compound of Formula XX in which X is a bond, is a known compound that can be prepared according to the literature procedure: Stillings, M. R. et al., *J. Med. Chem.*, 29, pp. 2280-2284 (1986).

When the carboxylic acid equivalent is an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br, the reaction is conveniently carried out by adding the acid halide to a solution of a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-

diamine of Formula XIX in a suitable solvent such as dichloromethane or 1,2-dichloroethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at a sub-ambient temperature.

The reaction with an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br may be carried out in two parts, which include (i) adding the acid halide to a solution of a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XIX in a suitable solvent such as chloroform, dichloromethane, 1,2-dichloroethane optionally in the presence of a tertiary amine such as triethylamine to afford an amide intermediate and (ii) cyclizing to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XX. The amide intermediate from part (i) can be optionally isolated using conventional techniques. The cyclization in part (ii) may be carried out by heating the amide intermediate from part (i) in a suitable solvent such as toluene. The cyclization in part (ii) can also be carried out in the presence of a base such as triethylamine or in the presence of an acid such as glacial acetic acid.

In step (5) of Reaction Scheme I, the hydroxy protecting group on a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XX is removed to reveal the hydroxy group in a product of Formula XXI. The deprotection reaction can be carried out using a variety of conventional methods, depending on the protecting group used. When P is a silyl group such as *tert*-butyldimethylsilyl, the deprotection can be carried out by adding tetrabutylammonium fluoride to a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XX in a suitable solvent such as tetrahydrofuran (THF). The reaction can be carried out at a sub-ambient temperature, such as –78 °C, and then warmed to ambient temperature. When the reaction is carried out in dichloromethane, a product of Formula XXII is typically isolated, and the reaction shown in step (6) may be obviated.

In step (6) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXI is cyclized by an intramolecular displacement of the halogen under basic conditions to provide a compound of Formula XXII. The reaction is conveniently carried out by adding a base such as potassium *tert*-butoxide to a solution of a compound of Formula XXI in a suitable solvent such as THF. The reaction can be carried out at ambient temperature or at an elevated temperature.

In step (7) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXIII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXII in a solvent such as chloroform or dichloromethane. The reaction can be carried out at ambient temperature.

In step (8) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXIII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXIV, a subgenus of Formulas I, II, and IIa. Step (8) involves the activation of an *N*-oxide of Formula XXIII 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 ammonium hydroxide to a solution of the *N*-oxide of Formula XXIII in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature.

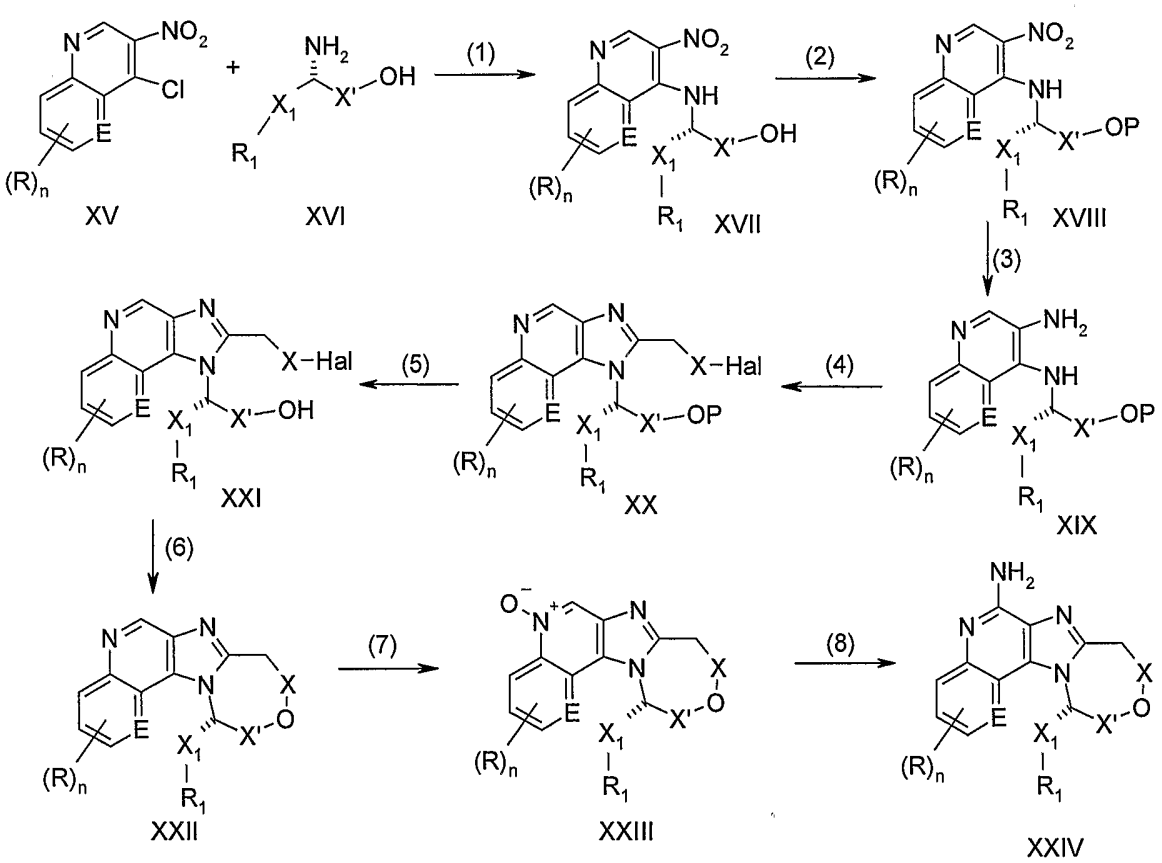
Alternatively, the oxidation and amination can be carried out as a one-pot procedure without isolating the *N*-oxide of Formula XXIII by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXII in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride.

The amination reaction in step (8) of Reaction Scheme I can alternatively be carried out by treating a 5*N*-oxide of Formula XXIII with trichloroacetyl isocyanate followed by hydrolysis of the resulting intermediate to provide a compound of Formula XXIV. The reaction is conveniently carried out in two steps by (i) adding trichloroacetyl isocyanate to a solution of a 5*N*-oxide of Formula XXIII in a solvent such as dichloromethane and stirring at ambient temperature to provide an isolable amide

intermediate. In step (ii), a solution of the intermediate in methanol is treated with a base such as sodium methoxide or ammonium hydroxide at ambient temperature.

A racemic mixture containing a compound of Formula XXIV may be obtained in this scheme if a racemic amino alcohol is used instead of a compound of Formula XVI. A racemic mixture thus prepared can be resolved by methods known to one skilled in the art, for example, by reacting the racemic mixture with an enantiomerially pure sulfonic acid or carboxylic acid and selectively crystallizing a salt of one of the enantiomers from the mixture. Alternatively, the enantiomer of a compound of Formula XXIV can be prepared using the enantiomer of the amino alcohol of Formula XVI in step (1) of Reaction Scheme I.

Reaction Scheme I



Compounds of the invention can also be prepared according to Reaction Scheme II, wherein R, R_1, R_2, X, X', X_1, Y, and Hal are as defined above; E and n are as defined in Reaction Scheme I; and Boc is *tert*-butoxycarbonyl.

In step (1) of Reaction Scheme II, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XV is treated with a Boc-protected diamine of Formula XXV to provide a compound of Formula XXVI. Boc-protected diamines of Formula XXV are available from the corresponding deprotected diamines, which are either commercially available or readily synthesized from amino alcohols of Formula XVI. The Boc protection can be carried out, for example, by treating a diamine such as 1,2-diaminopropane dihydrochloride with one equivalent of di-*tert*-butyl dicarbonate in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The protection reaction can be carried out at a sub-ambient temperature such as 0 °C and allowed to warm to ambient temperature. The reaction shown in step (1) of Reaction Scheme II is conveniently carried out under the conditions described in step (1) of Reaction Scheme I.

In steps (2) and (3) of Reaction Scheme II, a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XXVI is first reduced to a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XXVII, which is then treated with a halogen-substituted carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXVIII. Steps (2) and (3) of Reaction Scheme II can be carried out according to the methods described in steps (3) and (4) of Reaction Scheme I.

In step (4) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXVIII treated with acid to effect a removal of the Boc group and an intramolecular displacement of the halogen by the amino group to provide a compound of Formula XXIX. The reaction is conveniently carried out by treating the compound of Formula XXVIII with hydrogen chloride in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature or at an elevated temperature such as the reflux temperature of the solvent.

In step (5) of Reaction Scheme II, the secondary amine of a compound of Formula XXIX or a salt thereof is converted to an amide, sulfonamide, sulfamide, urea, or tertiary amine of Formula XXX using conventional methods. For example, a compound of Formula XXIX or a salt thereof can react with an acid chloride of Formula $R_2C(O)Cl$ to provide a compound of Formula XXX in which Y is -C(O)-. In addition, a compound of Formula XXIX can react with sulfonyl chloride of Formula $R_2S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_2S(O)_2)_2O$ to provide a compound of Formula XXX in which Y is

-$S(O)_2$-. Numerous acid chlorides of Formula $R_2C(O)Cl$, sulfonyl chlorides of Formula $R_2S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_2S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction is conveniently carried out by adding the acid chloride of Formula $R_2C(O)Cl$, sulfonyl chloride of Formula $R_2S(O)_2Cl$, or sulfonic anhydride of Formula $(R_2S(O)_2)_2O$ to a solution of the compound of Formula XXIX in a suitable solvent such as chloroform, dichloromethane, or *N,N*-dimethylformamide (DMF). Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C.

Ureas of Formula XXX, where Y is -C(O)-NH- can be prepared by reacting a compound of Formula XXIX or a salt thereof with isocyanates of Formula $R_2N=C=O$. Numerous isocyanates of Formula $R_2N=C=O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the isocyanate of Formula $R_2N=C=O$ to a solution of the compound of Formula XXIX in a suitable solvent such as DMF or chloroform. Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. Alternatively, a compound of Formula XXIX can be treated with an isocyanate of Formula $R_2(CO)N=C=O$, a thioisocyanate of Formula $R_2N=C=S$, a sulfonyl isocyanate of Formula $R_2S(O)_2N=C=O$, or a carbamoyl chloride of Formula R_2N-(R_8)-C(O)Cl to provide a compound of Formula XXX, where Y is -C(O)-N(R_8)-(CO)-, -C(S)-N(R_8)-, -C(O)-N(R_8)-$S(O)_2$-, or -C(O)-N(R_8)-, respectively. Alternatively, a compound of Formula XXIX can be treated with a carbamoyl chloride of Formula Cl-C(O)-heterocyclyl, wherein heterocyclyl is attached at a nitrogen atom, to provide a compound of Formula XXX, wherein Y is -C(O)- and R_2 is heterocyclyl attached at a nitrogen atom.

Sulfamides of Formula XXX, where Y is –$S(O)_2$-N(R_8)-, can be prepared by reacting a compound or salt of Formula XXIX with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula $HN(R_8)R_2$. Alternatively, sulfamides of Formula XXX can be prepared by reacting a compound of Formula XXIX with a sulfamoyl chloride of formula

$R_2(R_8)N\text{-}S(O)_2Cl$. Many sulfonyl chlorides of Formula $R_2S(O)_2Cl$ and amines of Formula $HN(R_8)R_2$, and some sulfamoyl chlorides of formula $R_2(R_8)N\text{-}S(O)_2Cl$ are commercially available; others can be prepared using known synthetic methods.

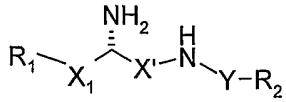
Compounds of Formula XXX where Y is a bond can be prepared by reductive alkylation of the secondary amine of compound of Formula XXIX. The alkylation is conveniently carried out in two parts by (i) adding an aldehyde or ketone to a solution of a compound of Formula XXIX or a salt thereof in a suitable solvent such as DMF or THF in the presence of a base such as *N,N*-diisopropylethylamine. In part (ii) the reduction is carried out by adding a suitable reducing agent such as the borane-pyridine complex. Both part (i) and part (ii) can be carried out at ambient temperature.

In steps (6) and (7) of Reaction Scheme II, a compound of Formula XXX is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXXI, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXXII, a subgenus of Formulas I, II, and IIa. Steps (6) and (7) of Reaction Scheme II can be carried out as described in steps (7) and (8) of Reaction Scheme I.

The reactions described in Reaction Scheme II may also be carried out in a different order. For example, in step (4) of Reaction Scheme II, a compound of XXVIII may be cyclized under basic conditions to provide a fused piperazine, [1,4]diazepane, [1,4]diazocane, or [1,5]diazocane ring wherein the secondary amine is still protected by the Boc group. The reaction is conveniently carried out by adding a base such as potassium *tert*-butoxide to a solution of a compound of Formula XXVIII in a suitable solvent such as THF. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as 0 °C. The resulting compound can then be oxidized and aminated according to the methods of steps (7) and (8) of Reaction Scheme I before the Boc group is removed under acidic conditions. The removal of the Boc group is conveniently carried out by adding a solution of hydrogen chloride in 1,4-dioxane or ethanol or a solution of trifluoroacetic acid in dichloromethane to the Boc-protected amine (i.e., a compound of Formula XXXII wherein Y is -C(O)-O- and R_2 is a *tert*-butyl group). The deprotection reaction may be run in a suitable solvent such as dichloromethane at ambient temperature or at an elevated temperature such as the reflux temperature of the solvent. The resulting secondary amine can then be treated according to one of the many

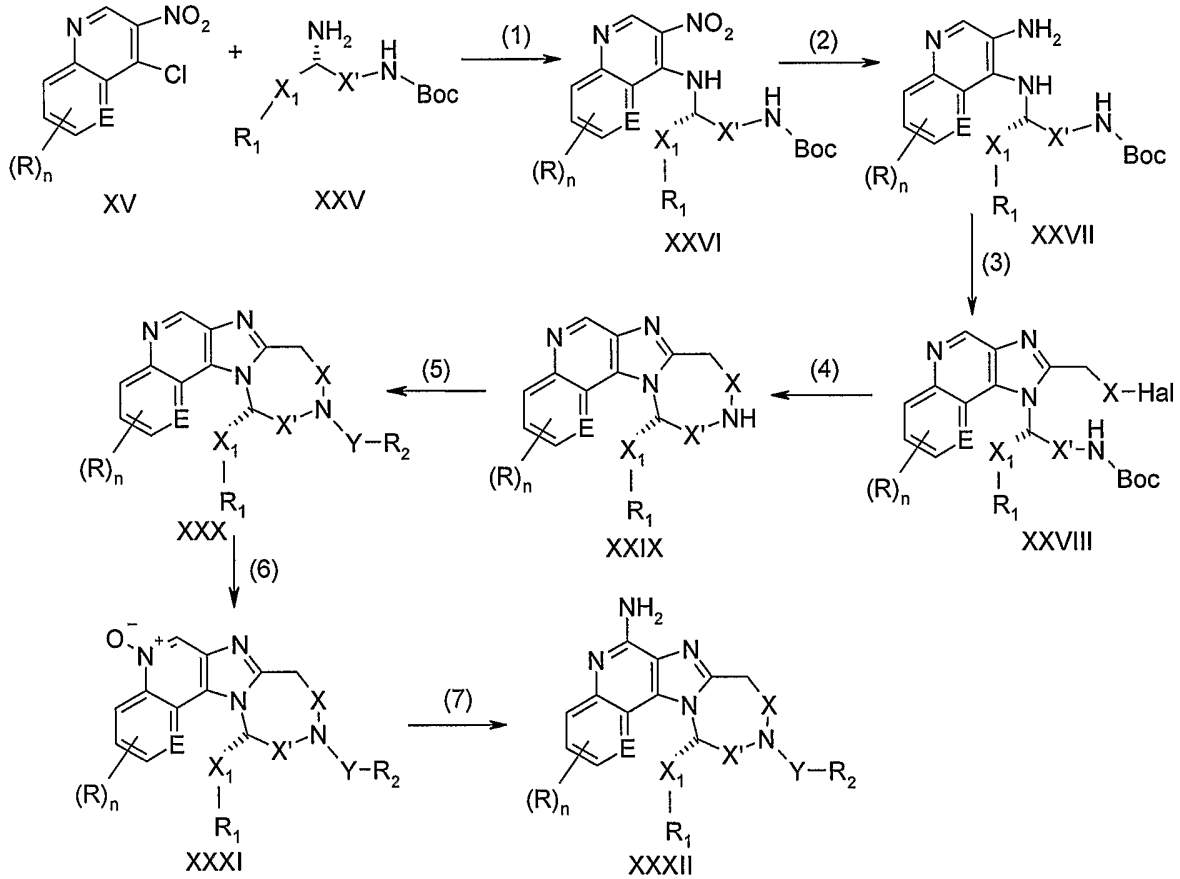
methods described in step (5) of Reaction Scheme II to provide a compound of Formula XXXII wherein Y and R_2 are as defined above.

Alternatively, instead of a Boc-protected diamine of Formula XXV, the reaction sequence shown in Reaction Scheme II can be carried out starting with the reaction of a compound of Formula XV with a compound of Formula



, which can be synthesized from the corresponding diamine using one of the various methods described in step (5) of Reaction Scheme II. The product can then be treated according to the methods described in steps (2), (3), (4), (6), and (7) in Reaction Scheme II to provide a compound of Formula XXXII.

Reaction Scheme II

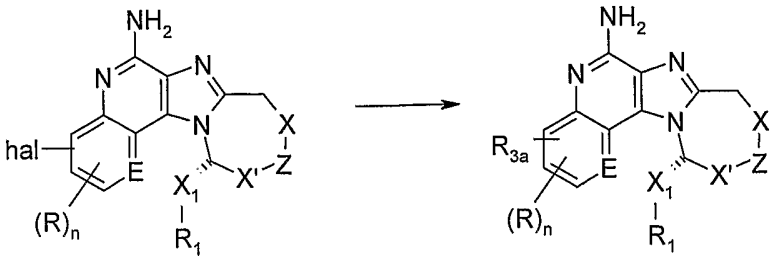


For some embodiments, compounds of the invention are prepared according to Reaction Scheme III, wherein R, R_1, X, X', X_1, and Z are as defined above; E is as defined in Reaction Scheme I; hal is bromo or iodo; n is 0 or 1; R_{3a} is –Z'-R_{4b}, -Z'-X"$_a$-R_4, -Z'-X"$_b$-Y'-R_4, or –Z'-X"$_b$-R_5; where Z' is a bond; X"$_a$ is alkenylene; X"$_b$ is arylene, heteroarylene, and alkenylene interrupted or terminated by arylene or heteroarylene; R_{4b} is aryl or heteroaryl where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in R_4 above; and R_4, R_5, and Y' are as defined above. Compounds of Formula XXXIII can be prepared by the methods shown in Reaction Scheme I or Reaction Scheme II beginning with a compound of Formula XV wherein n is other than 0 and one of the R groups present is hal.

In Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXXIII is coupled with a boronic acid of Formula R_{3a}-B(OH)$_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXXIV, which is a subgenus of Formulas I, II, and IIa. The Suzuki coupling is carried out by combining a compound of Formula XXXIII with a boronic acid or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base such as sodium carbonate in a suitable solvent such as *n*-propanol or solvent mixture such as *n*-propanol/water. The reaction can be carried out at an elevated temperature (e.g., 80 °C -100 °C or the reflux temperature). Many boronic acids of Formula R_{3a}-B(OH)$_2$, anhydrides thereof, and boronic acid esters of Formula R_{3a}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods. See, for example, Li, W. et al, *J. Org. Chem.*, *67*, 5394-5397 (2002).

Other coupling reactions such as the Heck reaction, the Stille coupling, and the Sonogashira coupling can be used to prepare compounds of Formula XXXIV. Also, compounds of Formula XXXIV, wherein R_{3a} is -Z-X"$_a$-R_4, -Z-X"$_b$-Y'-R_4, or -Z-X"$_b$-R_5 in which X"$_b$ is alkenylene interrupted or terminated by arylene or heteroarylene, can undergo reduction of the X"$_a$ or X"$_b$ alkenylene group. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof.

Reaction Scheme III



XXXIII XXXIV

Compounds of the invention can be prepared according to Reaction Scheme IV where R, R_1, X, X', X_1, P, and Hal are as defined above; E is as defined in Reaction Scheme I; n is 0 or 1; R_{3b} is $-R_4$, -X"-R_4, -X"-Y'-R_4, -X"-Y'-X"-Y'-R_4, or -X"-R_5, where R_4, X", Y', and R_5 are as defined above. In step (1) of Reaction Scheme IV, a benzyloxyaniline or benzyloxyaminopyridine of Formula XXXV is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XXXVI. The reaction is conveniently carried out by adding a solution of a compound of Formula XXXV to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 45 °C. Many anilines and aminopyridines of Formula XXXV are commercially available; others can be prepared by known synthetic methods. For example, benzyloxypyridines of Formula XXXV can be prepared using the method of Holladay et al., *Biorg. Med. Chem. Lett.*, *8*, pp. 2797-2802, (1998).

In step (2) of Reaction Scheme IV, an imine of Formula XXXVI undergoes thermolysis and cyclization to provide a compound of Formula XXXVII. The reaction is conveniently carried out in a medium such as DOWTHERM A heat transfer fluid at a temperature in the range of 200 °C and 250 °C.

In step (3) of Reaction Scheme IV, a compound of Formula XXXVII is nitrated under conventional nitration conditions to provide a benzyloxy-3-nitroquinolin-4-ol of Formula XXXVIII. The reaction is conveniently carried out by adding nitric acid to the compound of Formula XXXVII in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature such as 125 °C.

In step (4) of Reaction Scheme IV, a benzyloxy-3-nitroquinolin-4-ol or benzyloxy-3-nitro[1,5]naphthyridin-4-ol of Formula XXXVIII is chlorinated using conventional

chlorination chemistry to provide a benzyloxy-4-chloro-3-nitroquinoline or benzyloxy-4-chloro-3-nitro[1,5]naphthyridine of Formula XXXIX. The reaction is conveniently carried out by treating the compound of Formula XXXVIII with phosphorous oxychloride in a suitable solvent such as DMF. The reaction can be carried out at an elevated temperature such as 100 °C, and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme IV, a benzyloxy-4-chloro-3-nitroquinoline or benzyloxy-4-chloro-3-nitro[1,5]naphthyridine of Formula XXXIX is treated with an amino alcohol of Formula XVI to provide a benzyloxy-3-nitroquinolin-4-amine or benzyloxy-3-nitro[1,5]naphthyridin-4-amine of Formula XL. The reaction is conveniently carried out according to the methods described in step (1) of Reaction Scheme I.

In steps (6) and (7) of Reaction Scheme IV, the hydroxy group of a benzyloxy-3-nitroquinolin-4-amine or benzyloxy-3-nitro[1,5]naphthyridin-4-amine of Formula XL is protected to provide a compound of Formula XLI, which is reduced to provide a benzyloxyquinoline-3,4-diamine or benzyloxy[1,5]naphthyridine-3,4-diamine of Formula XLII. Steps (6) and (7) of Reaction Scheme IV can be carried out according to the methods described in steps (2) and (3) of Reaction Scheme I.

In steps (8) and (9) of Reaction Scheme IV, a benzyloxyquinoline-3,4-diamine or benzyloxy[1,5]naphthyridine-3,4-diamine of Formula XLII is treated with a halogen-substituted carboxylic acid equivalent to provide benzyloxy-1*H*-imidazo[4,5-*c*]quinoline or benzyloxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLIII, which can then undergo deprotection to provide a compound of Formula XLIV or XLV. Steps (8) and (9) of Reaction Scheme IV can be carried out according to the methods described in steps (4) and (5) of Reaction Scheme I.

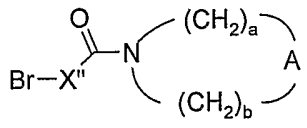
If a benzyloxy-substituted a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLIV is isolated from step (9), in step (10) of Reaction Scheme IV, the compound of Formula XLIV is cyclized by an intramolecular displacement of the halogen under basic conditions to provide a compound of Formula XLV. The reaction can be carried out under the conditions described in step (6) of Reaction Scheme I.

In step (11) of Reaction Scheme IV, the benzyl group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline or benzyloxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLV is cleaved to provide a 1*H*-imidazo[4,5-*c*]quinolinol or 1*H*-imidazo[4,5-

c][1,5]naphthyridinol of Formula XLVI. The cleavage is 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, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation is conveniently carried out by adding ammonium formate to a solution of a compound of Formula XLV in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is carried out at an elevated temperature, for example, the reflux temperature of the solvent.

In step (12) of Reaction Scheme IV a 1*H*-imidazo[4,5-*c*]quinolinol or 1*H*-imidazo[4,5-*c*][1,5]naphthyridinol of Formula XLVI is converted to an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLVII using a Williamson-type ether synthesis. The reaction is effected by treating a compound of Formula XLVI with an alkyl halide of Formula Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5 in the presence of a base. The reaction is conveniently carried out by combining the alkyl halide with a compound of Formula XLVI in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C. Alternatively, the reaction can be carried out by treating a solution of a compound of Formula XLVI in a solvent such as DMF with sodium hydride and then adding a reagent of Formula Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5.

Numerous reagents of Formulas Halide-R_4 and Halide-X"-Y'-R_4 are commercially available, for example, substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, substituted fluorobenzenes, bromo-substituted ketones, esters, and heterocycles. Other reagents of Formulas Halide-R_4, Halide-X"-Y'-R_4, and Halide-X"-R_5 can be prepared using conventional synthetic methods; for example, a bromo-substituted acid halide of Formula ClC(O)-X"-Br can be treated with a secondary amine in a suitable solvent such as dichloromethane to provide a variety of bromo-substituted amides of Formula Br-X"-C(O)-N(R_8)-R_4 or



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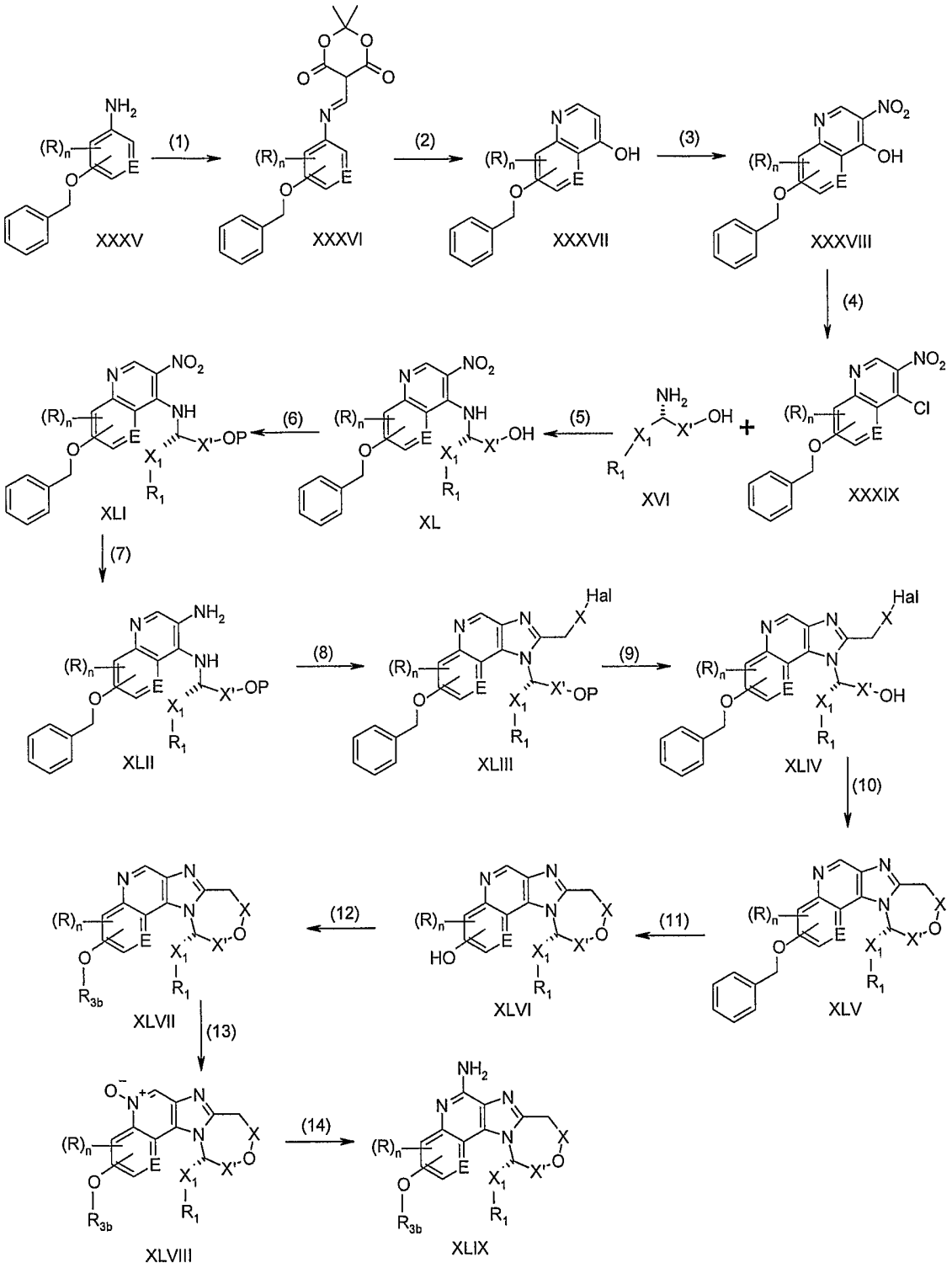
The reaction can be run at a sub-ambient temperature such as -25 °C. Also, compounds of Formula I-X"-N(R_8)-Boc are readily prepared in two steps from amino alcohols of Formula HO-X"-N(R_8)H by first protecting the amine with a Boc group and then converting the hydroxy group to an iodo group. Both reactions can be carried out using conventional methods. The compound of Formula XLVII wherein R_{3b} is -X"-Y'-R_4, wherein Y' is -N(R_8)-C(O)-O- and R_4 is *tert*-butyl thus prepared can be converted into a compound wherein Y' is -N(R_8)-Q- and Q and R_4 are as defined above using one of the methods described in step (5) of Reaction Scheme II.

Step (12) of Reaction Scheme IV can alternatively be carried out by treating a compound of Formula XLVI with an alcohol of Formula HO-X"-Y'-R_4, HO-X"-R_5, or HO-R_4 under Mitsunobu reaction conditions. Numerous alcohols of these formulas are commercially available; for example, 1-(3-hydroxypropyl)pyrrolidin-2-one, 1-(2-hydroxyethyl)pyrrolidin-2-one, and *tert*-butyl 4-hydroxypiperidine-1-carboxylate. Others can be prepared using conventional synthetic methods. The reaction is conveniently carried out by out by adding triphenylphosphine and an alcohol of Formula HO-X"-Y'-R_4, HO-X"-R_5, or HO-R_4 to a solution of a compound of Formula XLVI in a suitable solvent such as THF and then slowly adding diisopropyl azodicarboxylate or diethyl azodicarboxylate. The reaction can be carried out at ambient temperature or at a sub-ambient temperature, such as 0 °C.

In steps (13) and (14) of Reaction Scheme IV, an ether-substituted compound of Formula XLVII is first oxidized to a 5*N*-oxide of Formula XLVIII, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XLIX, a subgenus of Formulas I, II, and IIa. Steps (13) and (14) of Reaction Scheme IV can be carried out as described in steps (7) and (8) of Reaction Scheme I.

Isomers of the compound of Formula XXXV or Formula XXXVII, wherein E is nitrogen, can also be synthesized and can be used to prepare compounds of the invention according to the methods of Reaction Scheme IV.

Reaction Scheme IV



Imidazopyridines of the invention can be prepared according to Reaction Scheme V, where Hal, P, R_1, R_{A2}, R_{B2}, X, X', and X_1 are as defined above. In steps (1) and (2) of

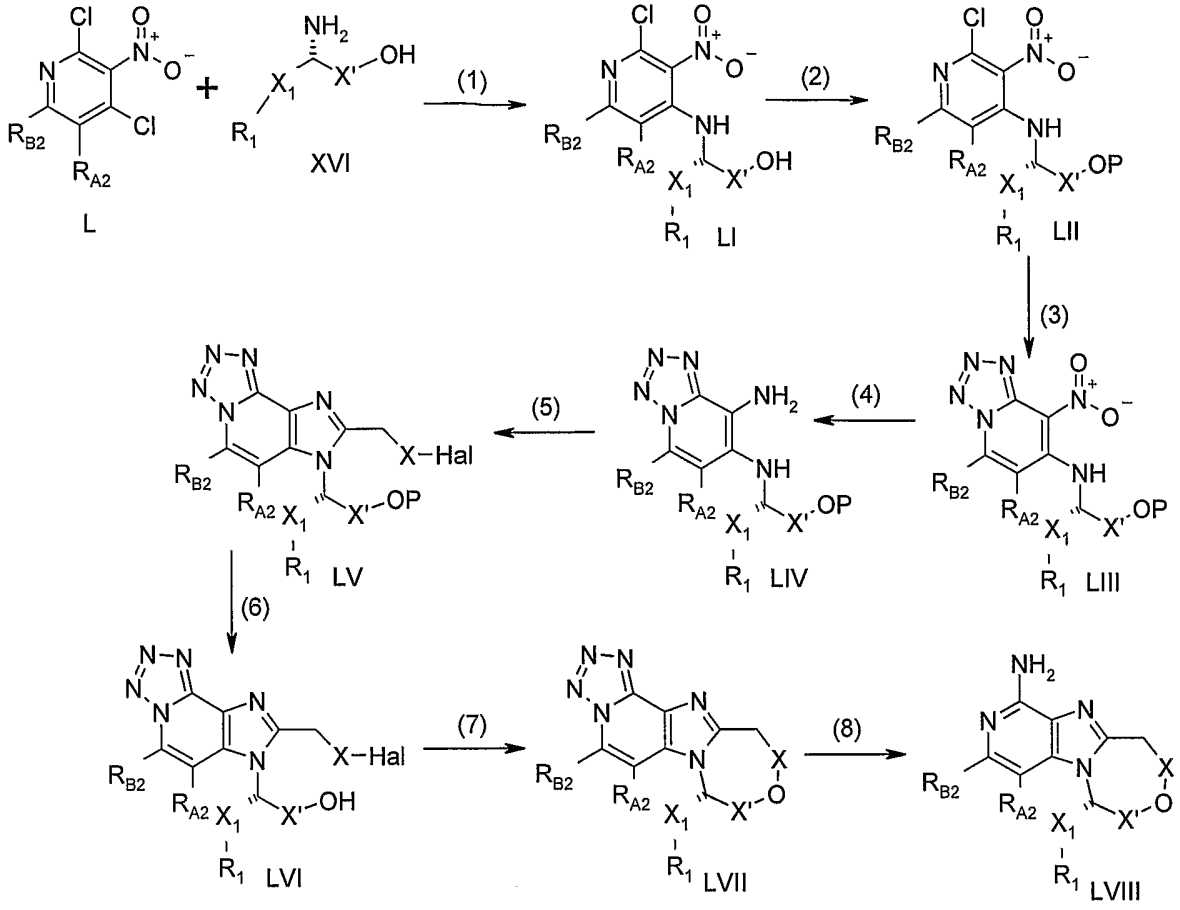
Reaction Scheme V, a 2,4-dichloro-3-nitropyridine of Formula L is reacted with an amino alcohol of Formula XVI to form a 2-chloro-3-nitropyridine of Formula LI, which then undergoes protection of the hydroxy group to provide a compound of Formula LII. Steps (1) and (2) of Reaction Scheme V are conveniently carried out according to the methods described in steps (1) and (2) of Reaction Scheme I. Many 2,4-dichloro-3-nitropyridines of the Formula L are known and can be readily prepared using known synthetic methods (see, for example, Dellaria et al, U.S. Pat. No. 6,525,064 and the references cited therein).

In step (3) of Reaction Scheme V, a 2-chloro-3-nitropyridine of Formula LII is reacted with an alkali metal azide to provide an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula LIII. The reaction can be carried out by combining the compound of Formula LII with an alkali metal azide, for example, sodium azide, in a suitable solvent such as acetonitrile/water, preferably 90/10 acetonitrile/water, in the presence of cerium(III) chloride, preferably cerium(III) chloride heptahydrate. Optionally, the reaction can be carried out with heating, for example, at the reflux temperature. Alternatively, the reaction can be carried out by combining the compound of Formula LII with an alkali metal azide, for example, sodium azide, in a suitable solvent such as DMF and heating, for example to about 50 °C to 60 °C, optionally in the presence of ammonium chloride.

Steps (4) through (7) of Reaction Scheme V can be carried out according to the methods described in steps (3) through (6) of Reaction Scheme I.

In step (8) of Reaction Scheme V, the tetrazolo ring is removed from a compound of Formula LVII by reaction with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate, which is then hydrolyzed to provide a compound of Formula LVIII, a subgenus of Formulas I, II, IIa, and VII. 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. The hydrolysis step 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.

Reaction Scheme V

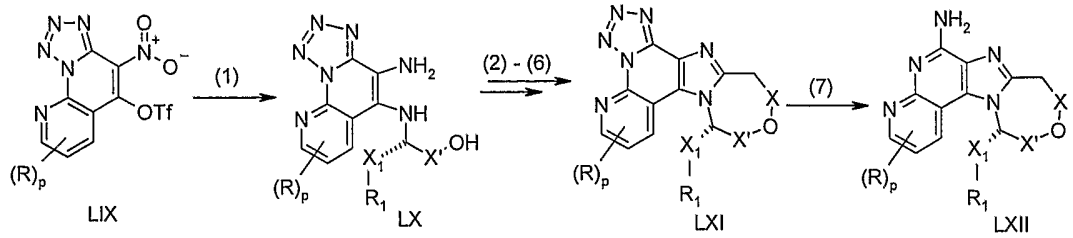


For some embodiments, naphthyridines of the invention can be prepared from tetrazolo compounds of Formulas LIX and LXIII according to Reaction Schemes VI and VII, wherein R_1, R, X, X', X_1, and p are as defined above, and -OTf is a trifluoromethanesulfonate group. Compounds of Formulas LIX and LXIII can be prepared by known synthetic routes; see, for example, U.S. Patent 6,194,425 (Gerster et al.). The tetrazolo compounds of Formulas LIX and LXIII can each be treated with an amino alcohol of Formula XVI according to the method of step (1) of Reaction Scheme I to provide compounds of Formulas LX and LXIV, respectively. A hydroxy-substituted tetrazolonaphthyridine of Formula LX or LXIV is converted to a compound of Formula LXI or LXV according to the methods of steps (2) through (6) of Reaction Scheme I.

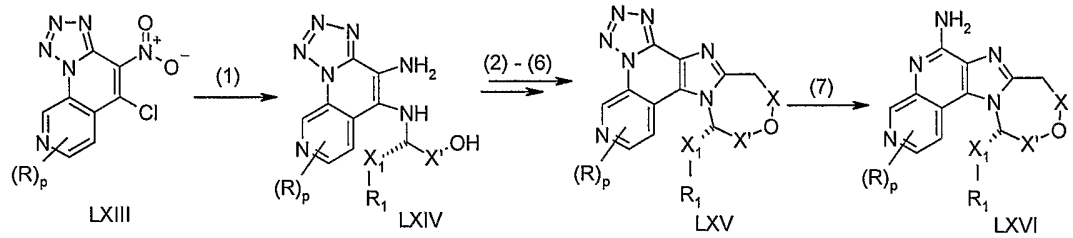
In step (7) of Reaction Scheme VI and VII, the tetrazolo group is removed from a compound of Formula LXI or LXV to provide a 1*H*-imidazo[4,5-*c*]naphthyridin-6-amine of Formula LXII or Formula LXVI. Removal of a tetrazolo group can be carried out in

two steps by first treating the compound of Formula LXI or LXV with triphenylphosphine and then hydrolyzing the resulting intermediate. The reaction conditions described in U.S. Patent 6,194,425 or the methods described in step (8) of Reaction Scheme V can be used.

Reaction Scheme VI



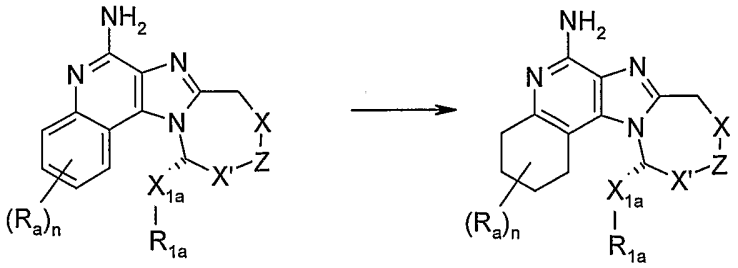
Reaction Scheme VII



Compounds of the invention can also be prepared according to Reaction Scheme VIII, wherein X, X', and Z are as defined above; n is an integer from 0 to 4; R_a is alkyl, alkoxy, hydroxy, or $-N(R_9)_2$; and X_{1a} and R_{1a} are subsets of X_1 and R_1 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. Compounds of Formula LXVII can be prepared according to the methods of Reaction Scheme I or Reaction Scheme II.

In Reaction Scheme VIII, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula LXVII is reduced to a tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula IVa, a subgenus of Formulas I, II., IIa, and IV. The reaction is conveniently carried out under hetereogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula LXVII in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature.

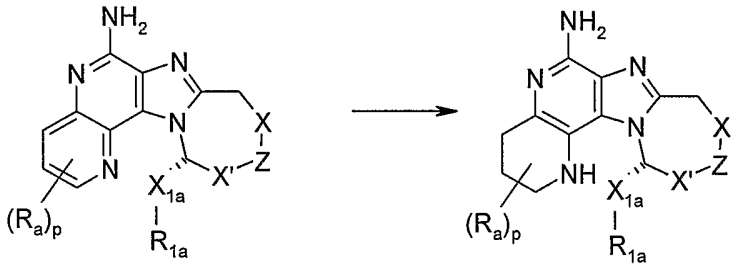
Reaction Scheme VIII



LXVII IVa

The reduction described in Reaction Scheme VIII can also be used to prepare a tetrahydro-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula VIa, as shown in Reaction Scheme IX, wherein X, X', Z, p, R_a, X_{1a}, and R_{1a} are as defined above. The product of Formula VIa is a subgenus of Formulas I, II, IIa, and VI.

Reaction Scheme IX



LXVIII VIa

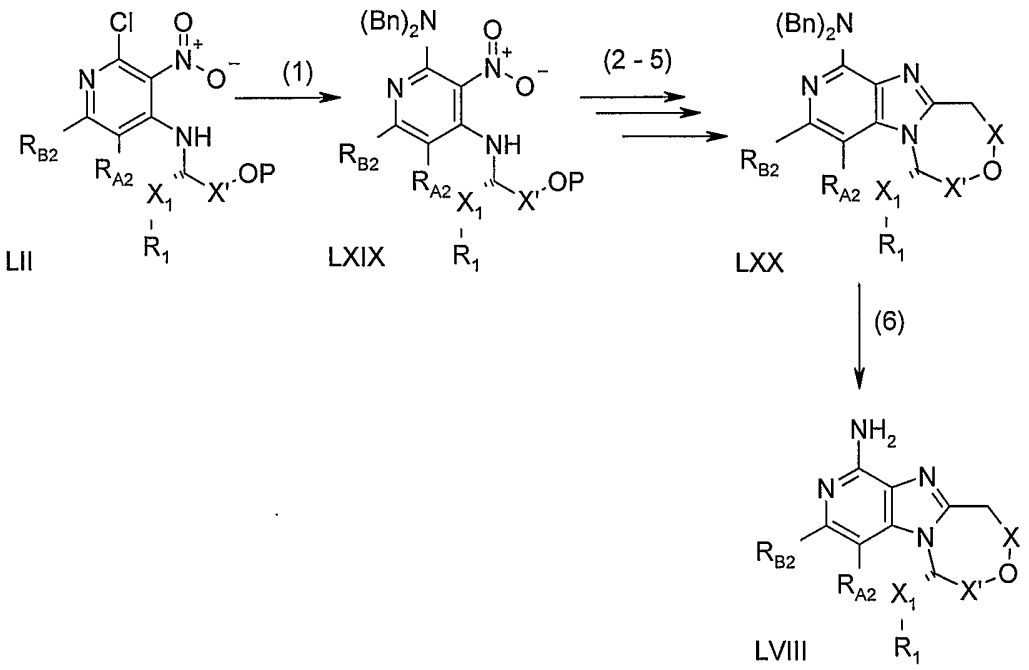
In some embodiments, compounds of the invention can be prepared according to Scheme X, wherein R_1, R_{A2}, R_{B2}, X, X', X_1, and P are as described above and Bn is benzyl. In step (1) of Reaction Scheme X, a 2-chloro-3-nitropyridine of Formula LII is treated with dibenzylamine to provide an N^2-dibenzyl-3-nitropyridin-2,4-diamine of Formula LXIX. The reaction can be carried out by combining the compound of Formula LII with dibenzylamine and a tertiary amine such as triethylamine in a suitable solvent such as toluene. The reaction can be carried out at an elevated temperature.

In steps (2), (3), (4), and (5) of Reaction Scheme X, an N^2-dibenzyl-3-nitropyridin-2,4-diamine of Formula LXIX is converted to a compound of Formula LXX using the methods described in steps (4), (5), (6), and (7) respectively of Reaction Scheme V.

In step (6) of Reaction Scheme X, the benzyl groups of a compound of Formula LXX are cleaved using transfer hydrogenation to provide a compound of Formula LVIII. The reaction can be carried out by adding ammonium formate to a solution of the

compound of Formula LXX in a suitable solvent such as ethanol or methanol in the presence of a catalyst such as palladium on carbon. The reaction can be carried out at an elevated temperature, for example, the reflux temperature of the solvent.

Reaction Scheme X



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme XI wherein R, X, Bn, E, and n are as defined above and

is a nitrogen containing heterocycle.

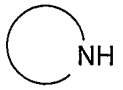
In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XV is treated with an amino alcohol of Formula LXXI to provide a compound of Formula LXXII. The reaction can be carried out as described in step (1) of Reaction Scheme I.

In steps (2) through (8) of Reaction Scheme XI, a compound of Formula LXXII is converted to compound of Formula LXXIII using the methods described in steps (2) through (8) of Reaction Scheme I.

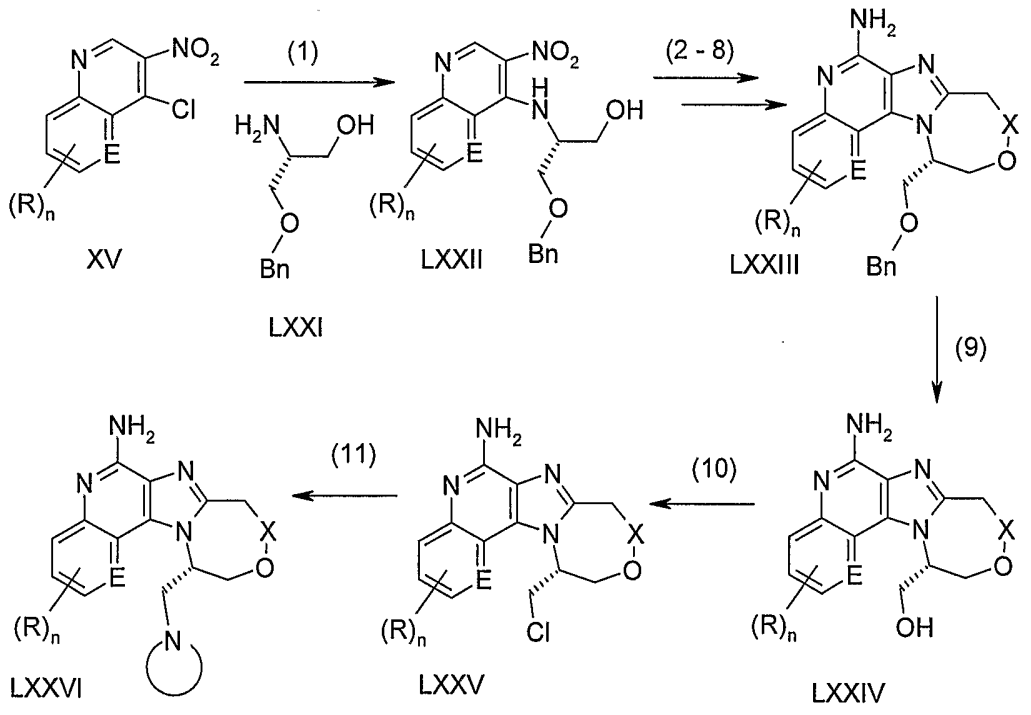
In step (9) of Reaction Scheme XI, the benzyl group of a compound of Formula LXXIII is cleaved to provide a hydroxy substituted compound of Formula LXXIV. The

cleavage can be carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as methanol.

In step (10) of Reaction Scheme XI, a hydroxy substituted compound of Formula LXXIV is chlorinated to provide a chloro substituted compound of Formula LXXV. The reaction can be carried out by combining the compound of Formula LXXIV with thionyl chloride and heating the mixture at an elevated temperature, for example, 70 °C.

In step (11) of Reaction Scheme XI, a chloro substituted compound of Formula LXXV is reacted with a nitrogen containing heterocycle of the Formula  to provide a compound of Formula LXXVI. The reaction can be carried out by heating a mixture of the compound of Formula LXXV and the heterocycle in a pressure vessel at an elevated temperature, such as, 150 °C. Examples of suitable heterocycles include morpholine, thiomorpholine, 2,6-dimethylmorpholine, piperidine, 4-benzylpiperidine, 4-hydroxypiperidine, 4-(2-hydroxyethyl)piperidine, 4-(1-pyrrolidinyl)piperidine, (R)-3-pyrroldinol, 4-piperidinecarboxamide, 1,2,3,4-tetrahydroisoquinoline, and thiazolidine.

Reaction Scheme XI



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme XII, wherein R, Bn, E, X, and n are as defined above and R_{1a} is phenyl which may be unsubstituted or substituted as described for R_1 above.

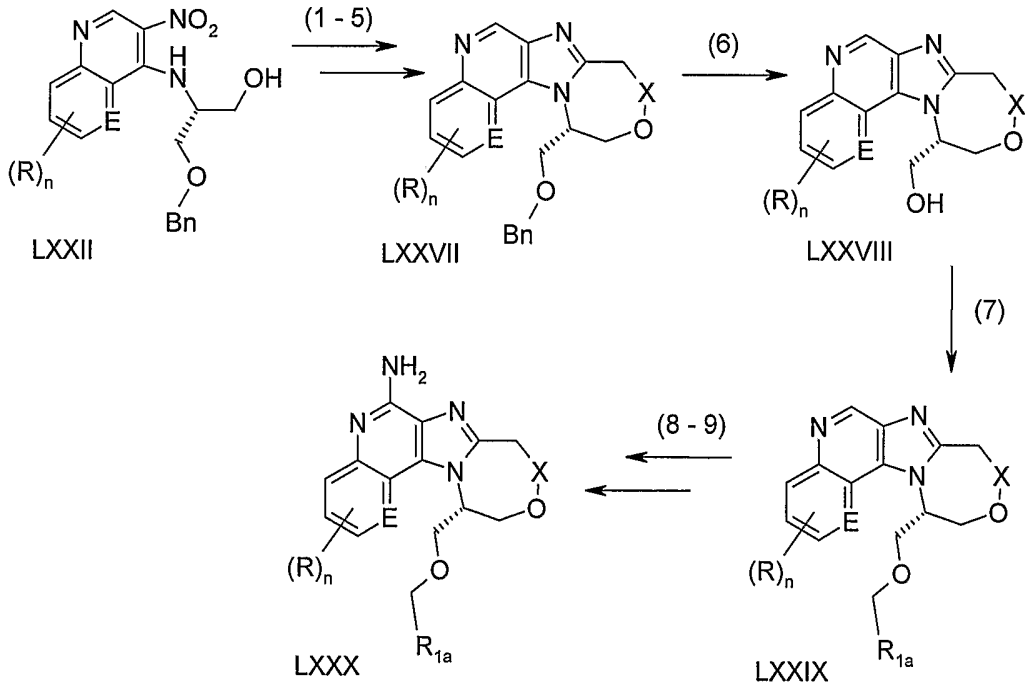
In steps (1) through (5) of Reaction Scheme XII, a compound of Formula LXXII is converted to a compound of Formula LXXVII using the methods describe in steps (2) through (6) of Reaction Scheme I.

In step (6) of Reaction Scheme XII, the benzyl group of a compound of Formula LXXVII is cleaved to provide a hydroxy substituted compound of Formula LXXVIII. The cleavage can be carried out using the method described in step (9) of Reaction Scheme XI.

In step (7) of Reaction Scheme XII, a hydroxy substituted compound of Formula LXXVIII is reacted with a benzyl bromide of the Formula R_{1a}-CH_2-Br to provide a benzyloxy substituted compound of Formula LXXIX. The reaction can be carried out by treating a solution of the compound of Formula LXXVIII in a suitable solvent, such as THF, with sodium hydride and then adding the benzyl bromide. The reaction can be carried out at ambient temperature or at a sub-ambient temperature, such as 0 °C.

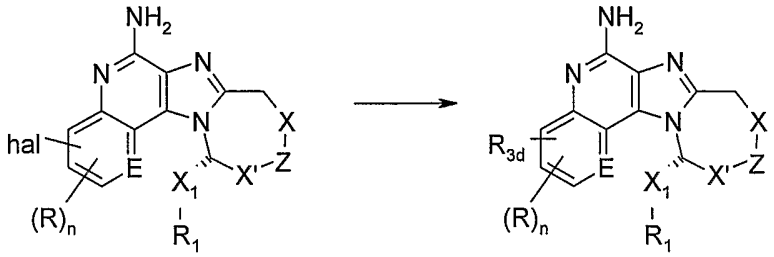
In steps (8) and (9) of Reaction Scheme XII, a compound of Formula LXXIX is converted to an amino substituted compound of Formula LXXX using the methods described in steps (7) and (8) respectively of Reaction Scheme I.

Reaction Scheme XII



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme XIII, wherein R, R_1, X, X', X_1, Z, hal, and n are as defined above and wherein R_{3d} is -heterocyclyl, -heterocyclylene-R_4, or -heterocyclylene-Y'-R_4, wherein R_4 and Y' are as defined above, and the heterocyclyl or heterocyclylene is attached to the quinoline or naphthyridine ring through a nitrogen atom. Compounds of Formula LXXXI can be prepared using a palladium-mediated coupling, which is carried out by combining a compound of the Formula XXXIII and the nitrogen-containing heterocyclyl compound in the presence of tris(dibenzylideneacetone)dipalladium, (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, sodium *tert*-butoxide, and a suitable solvent such as toluene. The reaction can be carried out at an elevated temperature such as 80 °C.

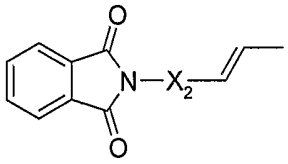
Reaction Scheme XIII



XXXIII LXXXI

In some embodiments, compounds of the invention can be prepared according to Reaction Scheme XIV, wherein hal, R_1, R_4, X, X', X_1, Y, and Z are as defined above and X_2 is a bond or C_{1-4} alkylene.

In step (1) of Reaction Scheme XIV, a compound of Formula LXXXII undergoes a Heck coupling reaction with an alkenyl-substituted phthalimide of the Formula



, which is commercially available or can be prepared using known synthetic methods. The reaction can be carried out by combining a compound of Formula LXXXII and the alkenyl substituted phthalimide in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base such as triethylamine or cesium carbonate in a suitable solvent such as acetonitrile, toluene, or DMF. The reaction can be carried out at an elevated temperature such as 85 °C to 125 °C under an inert atmosphere.

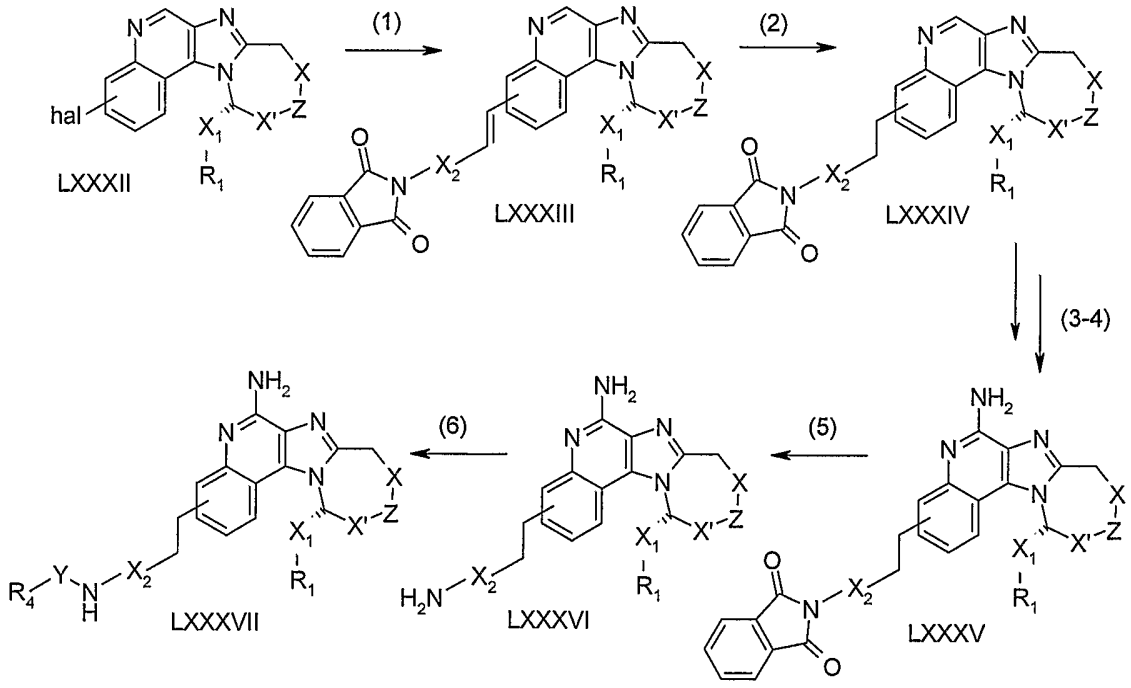
In step (2) of Reaction Scheme XIV, the alkenylene group is reduced to provide a compound of Formula LXXXIV. The reduction can be carried out as described in step (3) of Reaction Scheme I.

In steps (3) and (4) of Reaction Scheme XIV, a compound of Formula LXXXIV is oxidized and then aminated using the methods described in steps (7) and (8) respectively of Reaction Scheme I to provide a compound of Formula LXXXV.

In step (5) of Reaction Scheme XIV, the phthalimide group is removed from a compound of Formula LXXXV to provide an aminoalkyl substituted compound of Formula LXXXVI. The reaction can be carried out by adding hydrazine or hydrazine hydrate to a solution or suspension of a compound of Formula LXXXV in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature or at an elevated temperature, such as the reflux temperature of the solvent.

In step (6) of Reaction Scheme XIV, an aminoalkyl substituted compound of Formula LXXXVI is converted to a compound of Formula LXXXVII using the methods described in step (5) of Reaction Scheme II.

Reaction Scheme XIV



Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes I through XIV that would be apparent to one of skill in

the art. For example, the synthetic route shown in Reaction Scheme IV or Reaction Scheme V for the preparation of compounds wherein Z is -O- can be used to prepare compounds wherein Z is –N-Y-R_2- by using a Boc-protected diamine of Formula XXV in lieu of the amino alcohol of Formula XVI. In addition, the enantiomer of the products shown in Reaction Schemes I through IX or racemic mixtures can be prepared by using enantiomers of compounds of Formulas XVI or XXV or racemic reagents. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Prodrugs can be prepared in a variety of ways. For example, a compound with a hydroxy substituent may be converted to an ester, an ether, a carbonate, or a carbamate. For compounds containing an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as C_{1-6} alkanoyloxymethyl, 1-(C_{1-6} alkanoyloxy)ethyl, 1-methyl-1-(C_{1-6} alkanoyloxy)ethyl, C_{1-6} alkoxycarbonyloxymethyl, *N*-(C_{1-6} alkoxycarbonyl)aminomethyl, succinoyl, C_{1-6} alkanoyl, α-aminoC_{1-4} alkanoyl, arylacyl, -P(O)$(OH)_2$, -P(O)$(O\text{-}C_{1-6}$ alkyl$)_2$, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, and α-aminoacyl or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from racemic, D, and L-amino acids. For compounds containing an alcohol functional group, particularly useful prodrugs are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from naturally occurring L-amino acids.

Prodrugs can also be made from a compound containing an amino group by conversion of the amino group to a functional group such as an amide, carbamate, urea, amidine, or another hydroylizable group using conventional methods. A prodrug of this type can be made by the replacement of a hydrogen atom in an amino group, particularly the amino group at the 4-position, with a group such as –C(O)-R", α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R", -C(O)-N(R'")-R", –C(=NY_2)-R", -CH(OH)-C(O)-OY_2, -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, or -$CH(CH_3)Y_1$; wherein R" and R'" are each independently C_{1-10} alkyl, C_{3-7} cycloalkyl, or benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, haloC_{1-4} alkoxy,

-O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2;, with the proviso that R''' may also be hydrogen; each α-aminoacyl group is independently selected from racemic, D, or L-amino acids; Y_2 is hydrogen, C_{1-6} alkyl, or benzyl; Y_0 is C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, or di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl; and Y_1 is mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, or 4-C_{1-4} alkylpiperazin-1-yl. For compounds containing an amine functional group, particularly useful prodrugs are amides derived from carboxylic acids containing one to ten carbon atoms, amides derived from amino acids, and carbamates containing one to ten carbon atoms.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

The terms “a therapeutically effective amount” and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, computed according to the Dubois method, in which the body surface area of a subject (m^2) is computed using the subject's body weight: $m^2 = (wt\ kg^{0.425} \times height\ cm^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some

of these embodiments, the method includes administering sufficient compound to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/ m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce, and certain compounds or salts of the invention may inhibit, the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts or compositions are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention, particularly compounds or salts of Formulas II, IIa, III, IV, V, VI, VII, and IX, generally include interferon-α (IFN-α) and tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a

neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts described herein can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts described herein can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention, particularly compounds or salts of Formulas II-1, II-1a, III-1, IV-1, V-1, VI-1, VII-1, and IX-1, or compounds or salts of Formulas II, IIa, III, IV, V, VI, VII, and IX wherein Z is -N(-Y-R_2)-, include tumor necrosis factor-α (TNF-α). Among other effects, inhibition of TNF-α production can provide prophylaxis or therapeutic treatment of TNF-α mediated diseases in animals, making the compounds or salt useful in the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF-α biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for inhibition of TNF-α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for

example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments the induction or inhibition of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to

provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/ m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

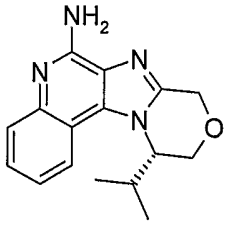
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

For Examples 1, 5, 6, 9, 10, 11, 13, and 23 the enantiomer of the compound was prepared in a separate experiment; see Examples 25 through 32. A mixture of the two enantiomers was prepared and analyzed by chiral stationary phase high-performance liquid chromatography using a Chiralcel OD-RH column, 0.46 mm x 15 cm, eluting with 30% methanol in pentane/methanol/triethylamine 90:10:0.2 (v/v/v) at a flow rate of 1.0 mL/min. Each of these examples was analyzed in comparison to the mixture of the two enantiomers, and the ratio favoring the enantiomer shown was greater than 99:1.

Example 1

(11*S*)-11-Isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A suspension of 3-chloro-4-nitroquinoline (4.16 g, 20.0 mmol) in 200 mL of CH_2Cl_2 was treated with triethylamine (5.56 mL, 40.0 mmol) under an atmosphere of N_2.

(2*S*)-2-Amino-3-methylbutan-1-ol (2.06 g, 20.0 mmol) was then added. The reaction mixture quickly turned yellow and the mixture was stirred overnight. The reaction mixture was then concentrated under reduced pressure to give a yellow solid. The resulting solid was partitioned between 100 mL of H_2O and 100 mL CH_2Cl_2. The layers were separated and the organic portion was washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give (2*S*)-3-methyl-2-[(3-nitroquinolin-4-yl)amino]butan-1-ol (3.97 g) as a yellow solid.

Part B

(2*S*)-3-Methyl-2-[(3-nitroquinolin-4-yl)amino]butan-1-ol (3.97 g, 14.4 mmol) was dissolved in 15 mL of dry pyridine and treated with *tert*-butyldimethylsilyl chloride (2.40 g, 15.9 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) (176 mg, 1.44 mmol). The reaction mixture was stirred under N_2 and heated to 56 °C. After 2 days, the reaction mixture was concentrated under reduced pressure. The resulting solid was partitioned between 100 mL of H_2O and 100 mL of ethyl acetate. The layers were separated and the organic portion was washed with H_2O and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave *N*-[(1*S*)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]-3-nitroquinolin-4-amine (5.46 g) as a yellow syrup.

Part C

N-[(1*S*)-1-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]-3-nitroquinolin-4-amine (5.46 g, 14.0 mmol) was dissolved in 50 mL of toluene and the solution was placed in a pressure bottle. Platinum on carbon (5%, 1.0 g) was then added and the reaction mixture was shaken under H_2 at 48 PSI (3.3×10^5 Pa). After 5 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with toluene and the combined filtrates were concentrated under reduced pressure to give N^4-[(1*S*)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]quinoline-3,4-diamine (5.05 g) as a brown foam.

Part D

N^4-[(1*S*)-1-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]quinoline-3,4-diamine (5.05 g, 14.0 mmol) was dissolved in 140 mL of dry 1,2-dichloroethane and the solution was stirred under N_2. Ethyl 2-chloroethanimidoate hydrochloride (3.33 g,

21.1 mmol) was then added and the reaction mixture was heated to 70 °C. After stirring for 2 days, the reaction mixture was cooled and treated with 70 mL of $CHCl_3$ and 100 mL of saturated sodium bicarbonate ($NaHCO_3$) solution. The layers were separated and the organic portion was washed with H_2O and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 33% - 50% ethyl acetate/hexanes) gave 1-[(1*S*)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (4.85 g) as a dull yellow solid.

Part E

1-[(1*S*)-1-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (4.85 g, 11.6 mmol) was dissolved in 110 mL of tetrahydrofuran (THF) and the solution was cooled to -78 °C under N_2. A 1.0 M solution of tetrabutylammonium fluoride in THF (12.8 mL) was added and the reaction mixture was allowed to warm to 0 °C overnight. The reaction mixture was then treated with 50 mL of saturated sodium bicarbonate solution and 100 mL of $CHCl_3$. The layers were separated and the organic portion was washed with H_2O (50 mL) and brine (4 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow syrup. The syrup was concentrated from toluene (3X) to give a pale yellow foam. This material was dissolved in 100 mL of anhydrous THF and the solution was cooled 0 °C and stirred under N_2. Solid potassium *tert*-butoxide was then added and the reaction mixture was allowed to warm to ambient overnight. The THF was then removed under reduced pressure and the resulting material was partitioned between 100 mL of $CHCl_3$ and 100 mL of saturated sodium bicarbonate solution. The layers were separated and the organic portion was washed with H_2O and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced to give brown foam. Chromatography (SiO_2, 0%-50% 80:18:2 $CHCl_3$/methanol/concentrated NH_4OH (CMA) in $CHCl_3$) gave(11*S*)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (2.13 g) as a light yellow solid.

Part F

(11*S*)-11-Isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (1.13 g, 4.23 mmol) was dissolved in 40 mL of CH_2Cl_2 and treated with 3-chloroperoxybenzoic acid (MCPBA) (1.13 g, 77% max). After stirring for 75 minutes, the

reaction was treated with 20 mL of 2% Na_2CO_3 solution and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 10 mL of brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (11*S*)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (1.20 g) as a crusty, off-white solid.

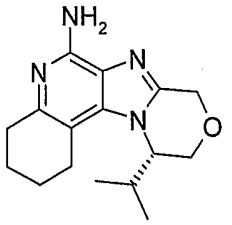
Part G

(11*S*)-11-Isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (1.20 g, 4.23 mmol) was dissolved in 50 mL of CH_2Cl_2 and treated with 5 mL of concentrated ammonium hydroxide solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (849 mg, 4.45 mmol) was carefully added. Rapid stirring was continued for 2 hours. The reaction mixture was then diluted with 25 mL of CH_2Cl_2 and 25 mL of H_2O. The layers were separated and the organic portion was washed with 2% Na_2CO_3 solution (3 x 25 mL), H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 5-25% CMA/$CHCl_3$) gave an off-white powder. Crystallization from ethyl acetate gave (11*S*)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (479 mg) as amber crystals, mp 249.0-250.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (t, *J* = 9.2 Hz, 2H), 7.52 (ddd, *J* = 1.2, 7.1, 8.3 Hz, 1H), 7.32 (ddd, *J* = 1.0, 7.2, 8.0 Hz, 1H), 5.38 (s, 2H), 5.17 (d, *J* = 15.8 Hz, 1H), 4.96 (d, *J* = 15.8 Hz, 1H), 4.61 (t, J = 3.8 Hz, 1H), 4.48 (d, J = 12.6 Hz, 1H), 4.05 (dd, J = 3.3, 12.5 Hz, 1H), 2.66 (m, 1H), 1.22 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 146.0, 144.8, 132.5, 127.3, 127.2, 122.3, 119.9, 115.6, 65.0, 63.8, 58.9, 31.4, 29.7, 19.4, 17.2; MS *m/z* 283 $(M + H)^+$. Anal. calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 67.85; H, 6.65; N, 20.01.

Example 2

(11*S*)-11-Isopropyl-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

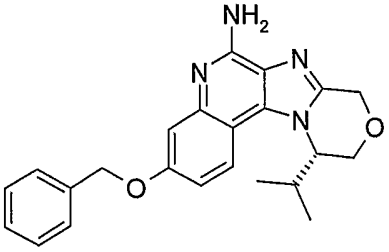


(11*S*)-11-Isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (320 mg, 1.13 mmol) was dissolved in 3 mL of trifluoroacetic acid and the solution was placed in a pressure bottle. Platinum oxide (250 mg) was then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa). After 20 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with a mixture of *iso*-propanol and CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure to give a syrup. The syrup was partitioned between H_2O and $CHCl_3$. The aqueous portion was made basic by addition of 10% NaOH solution until pH >12. The layers were separated and the organic portion was washed successively with 10% NaOH (2 x), H_2O and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a tan foam. Crystallization from ethyl acetate gave the title compound (215 mg) as light amber crystals, mp 158.0-160.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, J = 15.8 Hz, 1H), 4.86 (d, J = 15.7 Hz, 1H), 4.86 (s, 2H), 4.35 (d, J = 12.5 Hz, 1H), 4.30 (t, J = 4.0 Hz, 1H), 3.95 (dd, J = 2.5, 12.5 Hz, 1H), 2.95-2.80 (m, 4H), 2.35 (m, 1H), 2.00-1.71 (m, 4H), 1.09 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 147.8, 146.4, 138.3, 125.6, 107.6, 65.2, 64.4, 58.9, 33.9, 32.9, 24.4, 23.4, 23.3, 19.6, 17.8; MS *m/z* 287 $(M + H)^+$. Anal. calcd for $C_{16}H_{22}N_4O \cdot 0.28H_2O$: C, 65.94; H, 7.80; N, 19.23. Found: C, 66.25; H, 7.92; N, 19.47.

Example 3

(11*S*)-3-(Benzyloxy)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A mixture of triethyl orthoformate (92 mL, 0.55 mol) and 2,2-dimethyl-[1,3]-dioxane-4,6-dione (75.3 g, 0.522 mol) (Meldrum's acid) was heated at 55 °C for 90 minutes and then cooled to 45 °C. A solution of 3-benzyloxyaniline (100.2 g, 0.5029 mol) in methanol (200 mL) was slowly added to the reaction over a period 45 minutes while maintaining the reaction temperature below 50 °C. The reaction was then heated at 45 °C for one hour, allowed to cool to room temperature, and stirred overnight. The reaction mixture was cooled to 1 °C, and the product was isolated by filtration and washed with cold ethanol (~400 mL) until the filtrate was colorless. 5-{[(3-Benzyloxy)phenylimino]methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g) was isolated as a tan, powdery solid.

^{1}H NMR (300MHz, DMSO-d_6) : δ 11.21 (d, J = 14.2 Hz, 1H), 8.61 (d, J = 14.2 Hz, 1H), 7.49-7.30 (m, 7H), 7.12 (dd, J = 8.1, 1.96 Hz, 1H), 6.91 (dd, J = 8.4, 2.1 Hz, 1H), 5.16 (s, 2H), 1.68 (s, 6H).

Part B

A mixture of 5-{[(3-benzyloxy)phenylimino]methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g, 0.483 mol) and DOWTHERM A heat transfer fluid (800 mL) was heated to 100 °C and then slowly added to a flask containing DOWTHERM A heat transfer fluid (1.3 L, heated at 210 °C) over a period of 40 minutes. During the addition, the reaction temperature was not allowed to fall below 207 °C. Following the addition, the reaction was stirred at 210 °C for one hour, and then allowed to cool to ambient temperature. A precipitate formed, which was isolated by filtration, washed with diethyl ether (1.7 L) and acetone (0.5 L), and dried in an oven to provide 76.5 g of 7-benzyloxyquinolin-4-ol as a tan powder.

^{1}H NMR (300MHz, DMSO-d_6) : δ 11.53 (s, 1H), 7.99 (dd, J = 2.4, 7.4Hz, 1H), 7.79 (d, J = 7.4Hz, 1H), 7.50-7.32 (m, 5H), 7.00 (s, 1H), 6.98 (dd, J = 2.5, 7.4Hz, 1H), 5.93 (d, J = 7.5Hz, 1H), 5.20 (s, 2H).

Part C

A mixture of 7-benzyloxyquinolin-4-ol (71.47 g, 0.2844 mol) and propionic acid (700 mL) was heated to 125 °C with vigorous stirring. Nitric acid (23.11 mL of 16 M) was slowly added over a period of 30 minutes while maintaining the reaction temperature between 121 °C and 125 °C. After the addition, the reaction was stirred at 125 °C for 1 hour then allowed to cool to ambient temperature. The resulting solid was isolated by filtration, washed with water, and dried in an oven for 1.5 days to provide 69.13 g of 7-benzyloxy-3-nitroquinolin-4-ol as a grayish powder.

^{1}H NMR (300MHz, DMSO-d_6) : δ 12.77 (s, 1H), 9.12 (s, 1H), 8.17 (dd, J = 3.3, 6.3Hz, 1H), 7.51-7.33 (m, 5H), 7.21-7.17 (m, 2H), 5.25 (s, 2H).

Part D

N,N-Dimethylformamide (DMF) (100 mL) was cooled to 0 °C, and phosphorous oxychloride (27.5 mL, 0.295 mol) was added dropwise. The resulting solution was stirred for 25 minutes and then added dropwise to a mixture of 7-benzyloxy-3-nitroquinolin-4-ol (72.87 g, 0.2459 mol) in DMF (400 mL). Following the addition, the reaction was heated at 100 °C for 5 minutes, cooled to ambient temperature, and poured into ice water with stirring. A tan precipitate formed, which was isolated by filtration and dissolved in dichloromethane. The resulting solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 72.9 g of 7-benzyloxy-4-chloro-3-nitroquinoline as a light brown solid.

^{1}H NMR (300MHz, DMSO-d_6) : δ 9.34 (s, 1H), 8.36 (d, J = 8.7Hz, 1H), 7.71 (d, J = 2.4Hz, 1H), 7.66 (dd, J = 2.4, 9.3Hz, 1H), 7.56-7.51 (m, 2H), 7.46-7.34 (m, 3H), 5.40 (s, 2H).

Part E

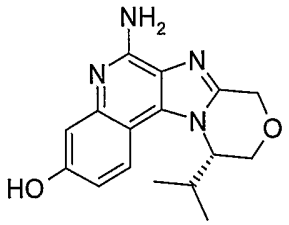
The title compound was prepared from 7-benzyloxy-3-chloro-4-nitroquinoline and (2*S*)-2-amino-3-methylbutan-1-ol following Parts A through G listed for the preparation of Example 1 with the modification that Parts F and G were carried out in $CHCl_3$ as the solvent. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white powder. The white powder was slurried in 10 mL of $CHCl_3$ and filtered to give a white solid. The

white solid was dissolved in a mixture of CH_2Cl_2 and methanol and then concentrated and the resulting solid was dried under vacuum at 65 °C to give (11*S*)-3-(benzyloxy)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white solid, mp 227 – 229 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (d, J = 9.0 Hz, 1H), 7.49 (d, J = 7.3 Hz, 2H), 7.40 (m, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.14 (d, J = 2.6 Hz, 1H), 6.99 (dd, J = 8.9, 2.6 Hz, 1H), 6.55 (s, 2H), 5.21 (s, 2H), 5.04 (d, J = 15.5 Hz, 1H), 4.90 (d, J = 15.5 Hz, 1H), 4.79 (m, 1H), 4.40 (d, J = 12.6 Hz, 1H), 4.04 (dd, J = 12.6, 3.3 Hz, 1H), 2.41 (m, 1H), 1.12 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.5, 152.6, 146.8, 145.6, 137.7, 132.3, 128.8, 128.1, 127.9, 125.5, 121.8, 112.3, 109.4, 109.0, 69.5, 64.5, 63.7, 57.8, 31.3, 19.2, 17.4; MS (ESI) *m/z* 389 $(M + H)^+$. Anal. calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23: N, 14.42. Found: C, 70.83; H, 5.88; N, 14.40.

Example 4

(11*S*)-6-Amino-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-ol



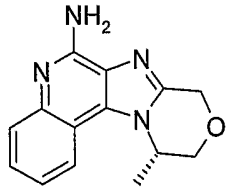
(11*S*)-3-(Benzyloxy)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (800 mg, 2.05 mmol) was dissolved in 260 mL of ethanol and the solution was placed in a pressure bottle. Palladium on carbon (10%, 460 mg) was then added and the reaction mixture was shaken under H_2 at 48 PSI (3.3 x 10^5 Pa) overnight. The reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with 1:1 CH_2Cl_2/ethanol and the combined filtrates were concentrated under reduced pressure to give an off-white solid. Chromatography (SiO_2, 20-40% CMA/$CHCl_3$) gave the desired product (370 mg) as an off-white solid, mp 210 – 215 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.52 (br s, 1H), 7.71 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.81 (dd, J = 8.8, 2.5 Hz, 1H), 6.48 (s, 2H), 5.03 (d, J = 15.4 Hz, 1H), 4.89 (d, J

= 15.4 Hz, 1H), 4.75 (m, 1H), 4.40 (d, J = 12.6 Hz, 1H), 4.03 (dd, J = 12.6, 3.3 Hz, 1H), 2.42 (m, 1H), 1.12 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.6, 152.4, 147.0, 145.1, 132.5, 125.0, 121.7, 112.4, 110.0, 108.4, 64.5, 63.7, 57.8, 31.2, 19.2, 17.4; MS (ESI) m/z 299 $(M + H)^+$. Anal. calcd for $C_{16}H_{18}N_4O_2 \cdot 0.61$ H_2O: C, 62.13; H, 6.26; N, 18.11. Found: C, 61.75; H, 6.10; N, 17.93.

Example 5

(11*S*)-11-Methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

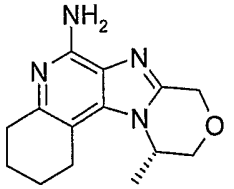


The title compound was prepared from 3-chloro-4-nitroquinoline and (*S*)-2-amino-1-propanol following Parts A through G listed for the preparation of Example 1 with the modification that Part F was carried out in $CHCl_3$ as the solvent. Crystallization from 1,2-dichloroethane gave (11*S*)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-c]quinolin-6-amine as an off-white solid, mp 280 – 282 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.44 (m, 1H), 7.28 (m, 1H), 6.60 (s, 2H), 5.08 (m, 2H), 4.95 (d, J = 15.6 Hz, 1H), 4.12 (m, 2H), 1.56 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.2, 145.4, 145.0, 131.6, 126.9, 126.6, 121.6, 120.7, 114.8, 68.7, 65.1, 50.5, 19.3; MS m/z 255 $(M + H)^+$. Anal. calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.82; H, 5.58; N, 21.98.

Example 6

(11*S*)-11-Methyl-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

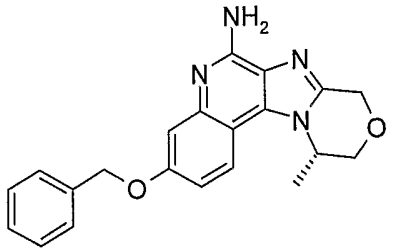


(11*S*)-11-Methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-c]quinolin-6-amine (1.13 g, 4.45 mmol) was dissolved in 20 mL of trifluoroacetic acid and the solution was placed in a pressure bottle. Platinum oxide (1.34 g) was then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa). After 2 days, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with 1,2-dichloroethane and the combined filtrates were concentrated under reduced pressure to give a peach colored oil. The oil was partitioned between dilute NH_4OH solution and CH_2Cl_2. The layers were separated and the organic portion was washed successively with dilute NH_4OH solution and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a white foam. Chromatography (SiO_2, 10-30% CMA/$CHCl_3$) gave (11*S*)-11-methyl-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (0.57 g) as a white solid, mp 209 – 211 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 5.75 (s, 2H), 4.97 (d, J = 15.6 Hz, 1H), 4.84-4.75 (m, 2H), 3.99 (s, 2H), 2.99 (m, 1H), 2.91 (m, 1H), 2.67 (m, 2H), 1.78 (m, 4H), 1.43 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.3, 145.2, 143.5, 135.9, 123.6, 104.3, 67.5, 63.6, 48.7, 31.2, 21.9, 21.8, 21.7, 19.7; MS *m/z* 259 $(M + H)^+$. Anal. calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 64.87; H, 7.22; N, 21.59.

Example 7

(11*S*)-3-(Benzyloxy)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

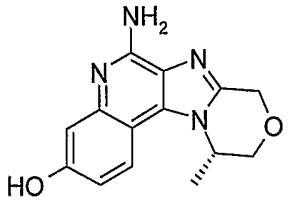


The title compound was prepared from 7-benzyloxy-3-chloro-4-nitroquinoline and (*S*)-2-amino-1-propanol following Parts A through G listed for the preparation of Example 1 with the modification that Parts F and G were carried out in $CHCl_3$ as the solvent. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white powder. The white powder was slurried in 10 mL of $CHCl_3$ and filtered to give a white solid. The white solid was dissolved in a mixture of CH_2Cl_2 and methanol and then concentrated to give (11*S*)-3-(benzyloxy)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white solid, mp 218 – 220 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 8.9 Hz, 1H), 7.49 (m, 2H), 7.43 – 7.33 (m, 3H), 7.15 (d, J = 2.5 Hz, 1H), 7.00 (dd, J = 8.9, 2.5 Hz, 1H), 6.52 (s, 2H), 5.21 (s, 2H), 5.06 (m, 2H), 4.91 (d, J = 15.5 Hz, 1H), 4.10 (m, 2H), 1.52 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.6, 152.5, 146.8, 144.6, 137.7, 132.0, 128.8, 128.1, 128.0, 125.4, 121.8, 112.4, 109.1, 108.9, 69.5, 68.7, 65.1, 50.3, 19.2; MS (ESI) *m/z* 361 (M + H)$^+$. Anal. calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.54. Found: C, 69.30; H, 5.48; N, 15.38.

Example 8

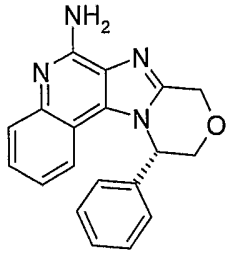
(11*S*)-6-Amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-ol



(11*S*)-3-(Benzyloxy)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (770 mg, 2.05 mmol) was dissolved in 200 mL of ethanol and the solution was placed in a pressure bottle. Palladium on carbon (10%, 430 mg) was then added and the reaction mixture was shaken under H_2 at 48 PSI (3.3 x 10^5 Pa) for 3 days. The reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with 1:1 CH_2Cl_2/ethanol and the combined filtrates were concentrated under reduced pressure to give an off-white solid. Chromatography (SiO_2, 30-50% CMA/$CHCl_3$) gave an off-white solid. Recrystallization from acetonitrile and methanol gave (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-ol (110 mg) as a white powder. mp > 250°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.49 (br s, 1H), 7.81 (d, J = 8.9 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 8.9, 2.5 Hz, 1H), 6.42 (s, 2H), 5.05 (d, J = 15.4 Hz, 1H), 5.00 (m, 1H), 4.91 (d, J = 15.4 Hz, 1H), 4.10 (m, 2H), 1.52 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.7, 152.3, 147.0, 144.2, 132.2, 125.0, 121.6, 112.4, 110.1, 108.2, 68.8, 65.1, 50.3, 19.2; MS (ESI) *m/z* 271 $(M + H)^+$. Anal. calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.99; H, 5.05; N, 20.62.

Example 9

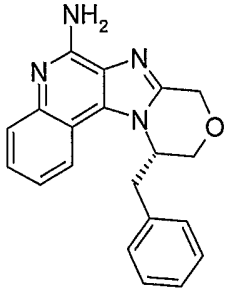
(11*S*)-11-Phenyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



The title compound was prepared from 3-chloro-4-nitroquinoline and (2*S*)-2-amino-2-phenylethanol following Parts A through G listed for the preparation of Example 1 with the modification that Part C was carried out in acetonitrile as the solvent and Part F was carried out in $CHCl_3$ as the solvent. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white solid. A second chromatography (SiO_2, 50% methanol/$CHCl_3$) gave (11*S*)-11-phenyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white solid. mp 284 – 286 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60 (m, 1H), 7.54 (m, 1H), 7.29 (m, 4H), 7.06 (m, 2H), 7.00 (m, 1H), 6.64 (s, 2H), 6.26 (m, 1H), 5.23 (d, J = 15.6 Hz, 1H), 5.09 (d, J = 15.6 Hz, 1H), 4.43 (dd, J = 12.0, 3.3 Hz, 1H), 4.22 (d, J = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.2, 146.3, 145.1, 139.8, 132.2, 129.1, 128.1, 126.9, 126.8, 126.5, 126.3, 121.1, 120.9, 114.7, 70.7, 65.3, 58.0; MS (ESI) *m/z* 317 $(M + H)^+$. Anal. calcd for $C_{19}H_{16}N_4O$: C, 72.14; H, 5.10; N, 17.71. Found: C, 71.81; H, 4.97; N, 17.44.

Example 10

(11*S*)-11-Benzyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



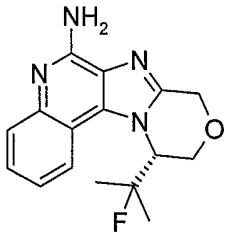
The title compound was prepared from 3-chloro-4-nitroquinoline and (2*S*)-2-amino-3-phenylpropan-1-ol following Parts A through G listed for the preparation of Example 1 with the modification that Part F was carried out in $CHCl_3$ as the solvent.

Crystallization from 2-propanol followed by chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave (11*S*)-11-benzyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as an off-white solid, mp 170 – 177 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (d, J = 8.1 Hz, 1H), 7.98 (dd, J = 8.3, 1.0 Hz, 1H), 7.48 (m, 1H), 7.38 (m, 5H), 7.30 (m, 1H), 6.66 (s, 2H), 5.24 (d, J = 10.9 Hz, 1H), 5.11 (d, J = 15.5 Hz, 1H), 4.98 (d, J = 15.5 Hz, 1H), 4.01 (m, 2H), 3.27 (m, 1H), 3.14 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.3, 145.5, 145.1, 136.8, 131.7, 129.6, 129.1, 127.3, 127.0, 126.9, 126.7, 121.7, 120.6, 114.9, 65.1, 64.8, 55.2, 37.9; MS (ESI) *m/z* 331 (M + H)$^+$. Anal calcd for $C_{20}H_{18}N_4O$•0.10 H_2O: C, 72.31; H, 5.52; N, 16.87. Found: C, 72.04; H, 5.42; N, 16.65.

Example 11

(11*R*)-11-(1-Fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

tert-Butyl (4*R*)-4-(1-hydroxy-1-methylethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (3.80 g, 14.7 mmol), prepared by the method of Joullie, *Tetrahedron*, 52, pp. 11673-11694, (1996) was dissolved in 90 mL of anhydrous CH_2Cl_2. The solution was cooled to -78 °C under an atmosphere of N_2. (Diethylamino)sulfur trifluoride (DAST) (2.25 mL, 17.0 mmol) was added and the reaction was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated $NaHCO_3$ solution and the layers were separated. The organic portion was washed successively with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography (SiO_2, 7% EtOAc/hexanes) gave *tert*-butyl (4*R*)-4-(1-fluoro-1-methylethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (1.98 g) as a nearly colorless liquid.

Part B

tert-Butyl (4*R*)-4-(1-fluoro-1-methylethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (1.98 g, 7.59 mmol) was dissolved in 20 mL of ethanol and treated with a 4.3 M solution of HCl in ethanol (7.5 mL). The solution was heated to 100 °C for 1 hour. The reaction mixture was cooled and concentrated under reduced pressure to give a white solid. The white solid was applied to a SiO_2 column. Elution with 1:1 $CHCl_3$/CMA gave (2*R*)-2-amino-3-fluoro-3-methylbutan-1-ol (678 mg) as a colorless oil.

Part C

The title compound was prepared from 3-chloro-4-nitroquinoline and (2*R*)-2-amino-3-fluoro-3-methylbutan-1-ol following Parts A through G listed for the preparation of Example 1 with the following modification. In Part E, a solution of 1-[(1*S*)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-fluoro-2-methylpropyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (1.63 g, 3.78 mmol) in CH_2Cl_2 (100 mL) was cooled to –78 °C. A solution of tetrabutylammonium fluoride in THF (4.16 mL of 1.0 M) was added, and the reaction mixture was allowed to warm to room temperature overnight. The solution was cooled again to –78 °C, and additional tetrabutylammonium fluoride in THF (0.4 mL) was added, and the reaction mixture was allowed to warm to room temperature and stirred for one day. The reaction mixture was washed with saturated aqueous $NaHCO_3$ followed by brine (4 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, eluting with 3% methanol in $CHCl_3$) provided (11*R*)-11-(1-fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as a light yellow foam.

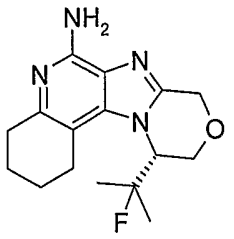
Crystallization of the final compound from ethyl acetate gave (11*R*)-11-(1-fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as peach colored crystals, mp 242-244 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (ddd, *J* = 1.2, 3.7, 8.3 Hz, 1H), 7.79 (dd, *J* = 1.0, 8.4 Hz, 1H), 7.49 (ddd, *J* = 1.4, 7.0, 8.4 Hz, 1H), 7.27 (ddd, *J* = 1.3, 7.0, 8.3 Hz, 1H), 5.37 (s, 2H), 5.22 (d, *J* = 16.2 Hz, 1H), 5.04 (dd, *J* = 2.5, 9.5 Hz, 1H), 5.04 (d, *J* = 16.1 Hz, 1H), 4.39 (d, *J* = 12.8 Hz, 1H), 4.10 (ddd, *J* = 3.0, 4.6, 12.8 Hz, 1H), 1.71 (d, *J* = 21.5 Hz, 3H), 1.27 (d, *J* = 23.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 145.4, 145.0, 134.1, 127.2, 126.9, 121.6, 121.4, 115.9, 97.9 (d, *J* = 172.8 Hz), 65.1 (d, *J* = 8.7 Hz), 65.0, 61.6 (d, *J* =

21.4 Hz), 25.7 (d, J = 23.6 Hz), 23.5 (d, J = 24.2 Hz); MS m/z 301 $(M + H)^+$. Anal. calcd for $C_{16}H_{17}FN_4O$: C, 63.99; H, 5.71; N, 18.65. Found: C, 63.62; H, 5.90; N, 18.40.

Example 12

(11*R*)-11-(1-Fluoro-1-methylethyl)-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



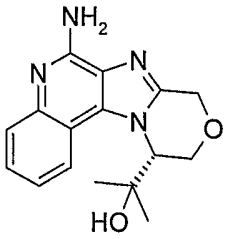
(11*R*)-11-(1-Fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (300 mg, 1.00 mmol) was dissolved in 10 mL of trifluoroacetic acid and the solution was placed in a pressure bottle. Platinum oxide (227 mg) was then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4 x 10^5 Pa). After 20 hours, an additional 200 mg of catalyst was added and the mixture was shaken under H_2 at 50 PSI (3.4 x 10^5 Pa) for an additional 24 h. The reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with a mixture of 2-propanol and CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure to give a syrup. The syrup was partitioned between H_2O and $CHCl_3$. The aqueous portion was made basic by addition of 10% NaOH solution until the pH was higher than 12. The layers were separated and the organic portion was washed successively with 10% NaOH (2 x), H_2O and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a tan foam. Chromatography (SiO_2, 25-33% CMA/$CHCl_3$) followed by crystallization from ethyl acetate gave (11*R*)-11-(1-fluoro-1-methylethyl)-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (159 mg) as off-white crystals, mp 195.5-197.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (d, J = 16.0 Hz, 1H), 4.93 (d, J = 16.0 Hz, 1H), 4.86 (s, 2H), 4.69 (dd, J = 1.9, 2.5 Hz, 1H), 4.27 (d, J = 12.8 Hz, 1H), 4.05 (ddd, J = 2.9, 4.7, 12.8 Hz, 1H), 3.20 (m, 1H), 2.93-2.77 (m, 2H), 2.65 (m, 1H), 1.95-1.64 (m, 4H), 1.61 (d, J = 27.7 Hz, 3H), 1.17 (d, J = 23.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.2,

145.9, 139.7, 125.6, 109.2, 97.7 (d, J = 171.8 Hz), 65.7 (d, J = 8.3 Hz), 65.3, 61.4 (d, J = 21.1 Hz), 33.1, 25.8 (d, J = 23.6 Hz), 24.7 (d, J = 11.2 Hz), 23.7 (d, J = 24.4 Hz), 23.5, 23.2; MS *m/z* 305 $(M + H)^+$. Anal. calcd for $C_{16}H_{21}FN_4O$: C, 62.22; H, 7.02; N, 18.14. Found: C, 62.02; H, 7.18; N, 18.36.

Example 13

2-[(11*R*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propan-2-ol



Part A

tert-Butyl (4*R*)-4-(1-hydroxy-1-methylethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (7.32 g, 27.8 mmol), prepared by the method of Joullie, *Tetrahedron*, 52, pp. 11673-11694, (1996), was dissolved in 20 mL of ethanol. A 4.3 M solution of hydrochloric acid in ethanol (15 mL) was then added and the reaction mixture was heated 85 °C. After 2 hours, the solution was cooled and concentrated under reduced pressure. The resulting residue was concentrated with 2-propanol several times and then with Et_2O to give crude (2*R*)-2-amino-3-methylbutane-1,3-diol hydrochloride (4.32 g) as a brown oil. This was used in the next reaction without further purification.

Part B

(2*R*)-2-amino-3-methylbutane-1,3-diol hydrochloride (4.32 g, 27.8 mmol) was dissolved in 10 mL of pyridine and the solution was stirred under N_2. *tert*-Butyldimethylsilyl chloride (16.8 g, 111 mmol) and DMAP (339 mg, 2.8 mmol) were then added and the reaction mixture was heated to 65 °C. After 3 days, the reaction was cooled and treated with in 3.5% NaH_2PO_4 solution. The solution was extracted with 200 mL CH_2Cl_2 and then with an additional 50 mL of CH_2Cl_2. The combined organic layers were washed with H_2O and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrate under reduced pressure. Chromatography (SiO_2, 3% MeOH/$CHCl_3$ with 0.1%

NH_4OH) gave (1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropylamine (5.85 g) as a light amber oil.

Part C

(1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropylamine (5.85 g, 16.9 mmol) was dissolved in 200 mL of anhydrous CH_2Cl_2 and the mixture was stirred under N_2. To this solution were added triethylamine (4.70 mL, 33.8 mmol) and 4-chloro-3-nitroquinoline (3.51 g, 16.9 mmol). The reaction mixture soon became bright yellow. After stirring for 3 days, the reaction mixture was concentrated under reduced pressure. The resulting yellow solid was partitioned between 200 mL H_2O and 200 mL CH_2Cl_2. The layers were separated and the organic portion was washed with H_2O and then brine. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting light brown oil was dissolved in about 200 mL of refluxing hexanes. A small amount of brown precipitate formed and was removed by filtration. The hexanes solution was concentrated to give a yellow solid. Chromatography (SiO_2, 10% ethyl acetate/CH_2Cl_2) gave *N*-[(1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]-3-nitroquinolin-4-amine (6.51 g) as a yellow solid.

Part D

N-[(1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]-3-nitroquinolin-4-amine (6.51 g, 12.5 mmol) was dissolved in 75 mL toluene and the solution was placed in a pressure bottle. Platinum on carbon (5%, 2.0 g) was then added and the reaction mixture was shaken under H_2 at 48 PSI (3.3×10^5 Pa). After 6 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with toluene and 2-propanol and the combined filtrates were concentrated under reduced pressure to give N^4-[(1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]quinoline-3,4-diamine (6.12 g) as a brown foam.

Part E

N^4-[(1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]quinoline-3,4-diamine (6.12 g, 12.5 mmol) was dissolved in 100 mL of dry 1,2-dichloroethane and the solution was stirred

under N_2. Ethyl 2-chloroethanimidoate hydrochloride (2.77 g, 17.5 mmol) was then added and the reaction mixture was heated to 70 °C. After stirring for 3 days, the reaction mixture was treated with an additional 1.00 g of ethyl 2-chloroethanimidoate hydrochloride and the reaction temperature was increased to 85 °C. After stirring for 2 days, the reaction was cooled and the 1,2-dichloroethane was removed under reduced pressure. The resulting material was partitioned between 200 mL of saturated $NaHCO_3$ solution and 200 mL of ethyl acetate. The layers were separated and the organic portion was washed with H_2O and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 25% -50% ethyl acetate/hexanes) gave 1-[(1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (1.74 g) as a golden syrup.

Part F

1-[(1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (1.74 g, 3.18 mmol) was dissolved in 80 mL of CH_2Cl_2 and the solution was cooled to -78° C under N_2. Tetrabutylammonium fluoride (1.0 M solution in THF, 3.50 mL) was added slowly and the stirred reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was then treated with an additional 0.3 mL of tetrabutylammonium fluoride solution and stirring was continued for 2 days. The reaction mixture was then treated with saturated $NaHCO_3$ solution, and the layers were separated. The organic portion was washed with brine (4 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 2-5% MeOH/$CHCl_3$) gave (11*R*)-11-(1-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (1.14 g) as a yellow syrup.

Part G

(11*R*)-11-(1-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (1.14 g, 2.91 mmol) was dissolved in 30 mL of THF and the stirred solution was cooled to -50 °C. Tetrabutylammonium fluoride (1.0 M solution in THF, 4.37 mL) was added slowly and the stirred reaction mixture was allowed top warm to ambient temperature over 4 hours. The reaction mixture was concentrated under reduced pressure and the resulting material was partitioned between 50

mL of CH_2Cl_2 and saturated $NaHCO_3$ solution. The layers were separated and the organic portion was washed with brine (4 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 8% MeOH/$CHCl_3$) gave 2-[(11*R*)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propan-2-ol (755 mg) as an off-white solid.

Part H

2-[(11*R*)-10,11-Dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propan-2-ol (755 mg, 2.67 mmol) was dissolved in 30 mL of CH_2Cl_2 and treated with MCPBA (57-86%, 806 mg). After stirring for 75 minutes, the reaction was treated with 50 mL of 2% Na_2CO_3 solution and the layers were separated. The aqueous layer was then extracted with 10% methanol/$CHCl_3$ (10 x 10 mL). The combined organic layers were washed with 10 mL of brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced to give 2-[(11*R*)-5-oxido-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propan-2-ol (798 mg) as a light yellow solid.

Part I

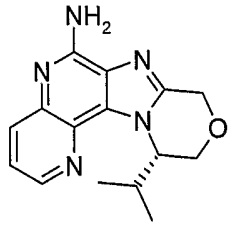
2-[(11*R*)-5-Oxido-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propan-2-ol (798 mg, 2.67 mmol) was dissolved in 25 mL of CH_2Cl_2 and treated with 5 mL of concentrated NH_4OH solution. The mixture was stirred rapidly and *p*-toluenesulfonyl chloride (534 mg, 2.80 mmol) was carefully added. Rapid stirring was continued for 2 hours. The reaction mixture was then treated with 25 mL of H_2O and the layers were separated. The aqueous portion was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 10% methanol/$CHCl_3$) gave a light yellow foam. Crystallization from ethyl acetate gave 2-[(11*R*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propan-2-ol (220 mg) as white crystals, mp 216-217 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (dd, J = 1.0, 8.4 Hz, 1H), 7.55 (dd, J = 1.1, 8.3 Hz, 1H), 7.35 (ddd, J = 1.3, 6.9, 8.4 Hz, 1H), 7.14 (ddd, J = 1.3, 7.0, 8.3 Hz, 1H), 6.45 (s, 2H), 5.12 (d, J = 16.0 Hz, 1H), 4.98 (d, J = 15.8 Hz, 1H), 4.95 (d, J = 1.7 Hz, 1H), 4.72 (s, 1H), 4.40 (d, J = 12.4 Hz, 1H), 4.02 (dd, J = 2.7, 12.6 Hz, 1H), 1.36 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 152.1, 146.5, 145.1, 134.1, 126.8, 126.4, 126.0, 123.6,

120.1, 116.3, 73.6, 65.3, 64.2, 62.3, 28.6, 27.0; MS *m/z* 299 $(M + H)^+$. Anal. calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.18; H, 5.93; N, 18.67.

Example 14

(11*S*)-11-Isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*][1,5]naphthyridin-6-amine

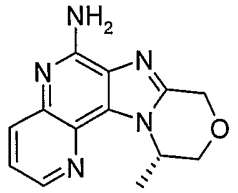


The title compound was prepared from 4-chloro-3-nitro[1,5]naphthyridine (see U.S. Patent No. 6,194,425, Example 29) and (2*S*)-2-amino-3-methylbutan-1-ol following Parts A through G listed for the preparation of Example 1 with the modification that Part F was carried out in $CHCl_3$ as the solvent. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave a light yellow solid. Recrystallization from 1,2-dichloroethane gave (11*S*)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*][1,5]naphthyridin-6-amine (0.72 g) as a white solid, mp 194 – 196 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (dd, J = 1.5, 4.3 Hz, 1H), 7.94 (dd, J = 1.5, 8.4 Hz, 1H), 7.44 (m, 1H), 6.92 (s, 2H), 5.13 (d, J = 15.9 Hz, 1H), 4.97 (m, 2H), 4.39 (d, J = 12.6 Hz, 1H), 4.04 (dd, J = 3.4, 12.6 Hz, 1H), 2.75 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.6, 147.2, 143.7, 140.3, 134.0, 132.9, 131.6, 129.5, 122.2, 64.4, 63.7, 58.5, 31.4, 19.4, 17.6; MS (ESI) *m/z* 284 $(M + H)^+$; Anal. calcd for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.40; H, 5.94; N, 25.00.

Example 15

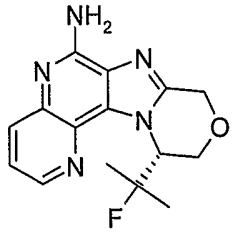
(11*S*)-11-Methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*][1,5]naphthyridin-6-amine



The title compound was prepared from 4-chloro-3-nitro[1,5]naphthyridine and (S)-(+)-2-amino-1-propanol following Parts A through G listed for the preparation of Example 1 with the modifications that in Part E the reaction with tetrabutylammonium fluoride was carried out in CH_2Cl_2 as the solvent, Part F was carried out in chloroform as the solvent, and Part G was carried out in 1,2-dichloroethane as the solvent. Chromatography (SiO_2, 10-30% CMA/$CHCl_3$) gave an off-white solid. Recrystallization from 1,2-dichloroethane gave (11*S*)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*][1,5]naphthyridin-6-amine (0.68 g) as a white crystalline solid, mp 240 – 242 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (dd, J = 1.5, 4.4 Hz, 1H), 7.92 (dd, J = 1.5, 8.4 Hz, 1H), 7.46 (m, 1H), 6.87 (s, 2H), 5.22 (m, 1H), 5.13 (d, J = 15.8 Hz, 1H), 4.97 (d, J = 15.8 Hz, 1H), 4.12 (m, 2H), 1.63 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 146.5, 143.8, 140.2, 133.8, 132.8, 131.2, 129.4, 122.2, 68.7, 64.9, 51.2, 19.9; MS (ESI) *m/z* 296 $(M + H)^+$; Anal. calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 60.93; H, 5.14; N, 27.62.

Example 16

(11*R*)-11-(1-Fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*][1,5]naphthyridin-6-amine

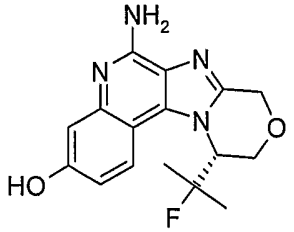


Part A

The title compound was prepared from 4-chloro-3-nitro[1,5]naphthyridine and (2*R*)-2-amino-3-fluoro-3-methylbutan-1-ol following Parts A through G listed for the preparation of Example 1 with the following modifications. Part D was carried out in propyl acetate as the solvent, and Part F was carried out in $CHCl_3$ as the solvent. Part E was carried out according to the modification described in Part C of Example 11. Chromatography on the final compound (SiO_2, 0-6% MeOH/CH_2Cl_2) afforded (11*R*)-11-(1-fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*][1,5]naphthyridin-6-amine (0.72 g) as an off-white solid, mp 192 – 194 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (dd, J = 1.5, 4.3 Hz, 1H), 7.91 (dd, J = 1.5, 8.4 Hz, 1H), 7.42 (m, 1H), 6.88 (s, 2H), 5.58 (dd, J = 2.3, 12.9 Hz, 1H), 5.17 (d, J = 16.1 Hz, 1H), 5.01 (d, J = 16.1 Hz, 1H), 4.45 (d, J = 12.6 Hz, 1H), 4.12 (dt, J = 3.1, 12.7 Hz, 1H), 1.42 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.4, 147.4, 143.0, 140.3, 134.2, 132.4, 129.4, 122.3, 97.3 (d, J = 174.6 Hz), 64.1, 63.8, 59.6 (d, J = 21.5 Hz), 25.5 (d, J = 23.5 Hz), 24.9 (d, J = 23.9 Hz); MS (ESI) *m/z* 302 $(M + H)^+$; Anal. calcd for $C_{15}H_{16}FN_5O$: C, 59.79; H, 5.35; N, 23.24. Found: C, 59.69; H, 5.14; N, 23.21.

Example 17

(11*R*)-6-Amino-11-(1-fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-ol



Part A

(11*R*)-3-(Benzyloxy)-11-(1-fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine was prepared from 7-(benzyloxy)-4-chloro-3-nitroquinoline and (2*R*)-2-amino-3-fluoro-3-methylbutan-1-ol following Parts A through G listed for the preparation of Example 1 with the modifications that Part C was carried out in acetonitrile as the solvent and Parts F and G were carried out in chloroform as the solvent. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) afforded (11*R*)-3-(benzyloxy)-11-(1-fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (310 mg) as an orange solid.

Part B

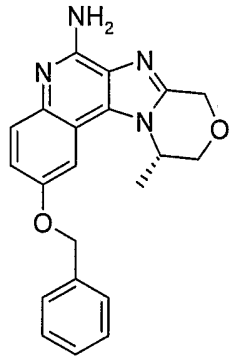
(11*R*)-3-(Benzyloxy)-11-(1-fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (310 mg, 0.763 mmol) was dissolved in ethanol (50 mL) and the solution was placed in a pressure bottle. Palladium on carbon (10%, 140 mg) was added and the reaction mixture was shaken under H_2 at 48 PSI (3.3×10^5 Pa) overnight. The reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with 1:1 CH_2Cl_2/ethanol and the combined filtrates were concentrated under reduced pressure to give an off white solid. Chromatography (SiO_2, 30-50% CMA/$CHCl_3$) followed by recrystallization from 1,2-dichloroethane gave (11*R*)-6-amino-11-(1-fluoro-1-methylethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-ol (63 mg) as a white powder, mp 219 – 221 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.97 (dd, J = 3.9, 9.0 Hz, 1H), 6.90 (d, J = 2.5 Hz, 1H), 6.69 (dd, J = 2.5, 9.0 Hz, 1H), 6.38 (s, 2H), 5.28 (m, 1H), 5.10 (d, J = 15.8 Hz, 1H), 4.97 (d, J = 15.8 Hz, 1H), 4.35 (d, J = 13.0 Hz, 1H), 4.10 (m, 1H), 1.64 (d, J =

22.1 Hz, 3H), 1.14 (d, J = 23.6 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.4, 152.2, 147.2, 144.9, 134.3, 125.0, 123.5 (d, J = 8.7 Hz), 111.4, 109.5, 109.1, 98.7 (d, J = 169.8 Hz), 64.9 (d, J = 8.1 Hz), 64.4, 60.3 (d, J = 20.3 Hz), 25.5 (d, J = 22.9 Hz), 23.7 (d, J = 23.9 Hz); MS (ESI) m/z 317 $(M + H)^+$; Anal. calcd for $C_{16}H_{17}FN_4O_2 \cdot 0.65\ H_2O \cdot 0.15\ C_2H_4Cl_2$: C, 57.10; H, 5.56; N, 16.34. Found: C, 57.09; H, 5.20; N, 16.20.

Example 18

(11*R*)-2-(Benzyloxy)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

6-(Benzyloxy)-4-chloro-3-nitroquinoline (see International Publication No. WO2005/020999, Example 57, Parts A through D) and (*S*)-(+)-2-amino-1-propanol were combined following Parts A through F listed for the preparation of Example 1, with the modification that Part F was carried out in $CHCl_3$ as the solvent, to give (11*S*)-2-(benzyloxy)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (2.02 g) as an orange foam.

Part B

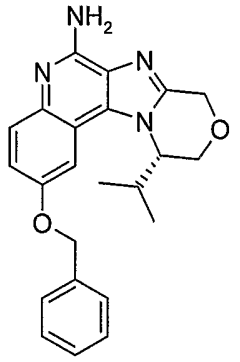
(11*S*)-2-(Benzyloxy)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (2.02 g, 5.59 mmol) and trichloroacetyl isocyanate (0.87 mL, 7.27 mmol) were dissolved in dichloromethane (50 mL) under an atmosphere of N_2. After one hour, the reaction was quenched with a small amount of methanol, and the solvent was removed under reduced pressure. The resulting residue was suspended in methanol (50 mL) and treated with NaOMe (25% in MeOH, 8 mL) for 20 hours. The volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane and water, adjusting to pH 11 with NH_4OH. The

aqueous layer was extracted with dichloromethane (3x). The combined organic layers were then washed with brine and dried over Na_2SO_4, filtered, and concentrated to give a light-brown foam. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave (11*R*)-2-(benzyloxy)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (1.35 g) as an off white solid, mp 100 – 120 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.58 (d, J = 9.1 Hz, 1H), 7.51 (m, 2H), 7.41 (m, 3H), 7.33 (m, 1H), 7.21 (dd, J = 2.6, 9.1 Hz, 1H), 6.37 (s, 2H), 5.25 (q, J = 12.2 Hz, 2H), 5.07 (m, 2H), 4.94 (d, J = 15.5 Hz, 1H), 4.12 (m, 2H), 1.45 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.3, 150.8, 145.5, 140.0, 137.7, 131.3, 128.9, 128.1, 127.9, 127.9, 127.2, 117.4, 114.8, 103.4, 70.0, 68.7, 65.1, 50.3, 19.4; MS (APCI) *m/z* 361 $(M + H)^+$; Anal. calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.54. Found: C, 69.86; H, 5.59; N, 15.64.

Example 19

(11*S*)-2-(Benzyloxy)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



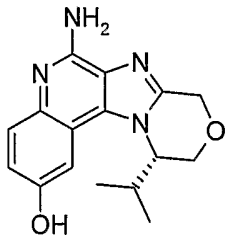
The title compound was prepared from 6-(benzyloxy)-4-chloro-3-nitroquinoline and (2*S*)-2-amino-3-methylbutan-1-ol following Parts A through F listed for the preparation of Example 1, with the modifications that Parts C and F were carried out in acetonitrile and $CHCl_3$, respectively, as the solvents, followed by Part B listed for the preparation of Example 18. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) followed by recrystallization from acetonitrile gave an off white solid. The material was dissolved in 1:1 dichloromethane/methanol and solvents were removed under reduced pressure (2x) to afforded (11*S*)-2-(benzyloxy)-11-isopropyl-10,11-dihydro-8*H*-

[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (1.04 g) as a white solid, mp 139 – 141 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (d, J = 9.1 Hz, 1H), 7.47 (m, 2H), 7.40 (m, 3H), 7.34 (m, 1H), 7.19 (dd, J = 2.6, 9.1 Hz, 1H), 6.37 (s, 2H), 5.29 (d, J = 11.9 Hz, 1H), 5.15 (d, J = 11.9 Hz, 1H), 5.07 (d, J = 15.5 Hz, 1H), 4.92 (m, 2H), 4.42 (d, J = 12.6 Hz, 1H), 4.06 (dd, J = 3.3, 12.6 Hz, 1H), 2.45 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.8, 150.4, 145.9, 139.7, 137.0, 131.2, 128.4, 127.7, 127.5, 126.8, 117.1, 114.6, 102.9, 69.6, 64.0, 63.1, 57.3, 31.2, 18.7, 16.9; MS (ESI) *m/z* 389 $(M + H)^+$; Anal. calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42. Found: C, 70.89; H, 6.08; N, 14.33.

Example 20

(11*S*)-6-Amino-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol



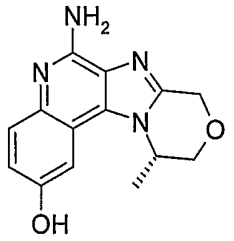
(11*S*)-2-(Benzyloxy)-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (530 mg, 1.36 mmol) was dissolved in ethanol (50 mL) and the solution was placed in a pressure bottle. Palladium on carbon (10%, 220 mg) was added and the reaction mixture was shaken under H_2 at 48 PSI (3.3 x 10^5 Pa) for 20 hours. The reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with 1:1 CH_2Cl_2/ethanol (200 mL) and the combined filtrates were concentrated under reduced pressure to give a white solid. Chromatography (SiO_2, 30-50% CMA/$CHCl_3$) gave (11*S*)-6-amino-11-isopropyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (240 mg) as a white powder, mp 208 – 210 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (br s, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.21 (d, J = 2.5 Hz, 1H), 6.98 (dd, J = 2.5, 8.9 Hz, 1H), 6.23 (s, 2H), 5.06 (d, J = 15.5 Hz, 1H), 4.92 (d, J = 15.5 Hz, 1H), 4.68 (t, J = 3.6 Hz, 1H), 4.42 (d, J = 12.6 Hz, 1H), 4.06 (dd, J = 3.3, 12.6

Hz, 1H), 2.45 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.2, 150.2, 146.2, 138.9, 131.5, 127.8, 127.2, 117.4, 115.6, 104.0, 64.5, 63.6, 58.0, 31.6, 19.3, 17.4; MS (APCI) m/z 299 $(M + H)^+$; Anal. calcd for $C_{16}H_{18}N_4O_2 \cdot 0.35\ H_2O$: C, 63.08; H, 6.19; N, 18.39. Found: C, 62.79; H, 6.23; N, 17.99.

Example 21

(11*S*)-6-Amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol

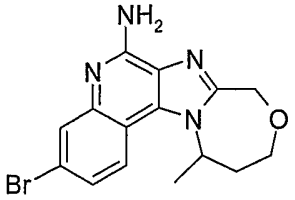


(11*R*)-2-(Benzyloxy)-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (840 mg, 2.33 mmol) was dissolved in ethanol (50 mL) and the solution was placed in a pressure bottle. Palladium on carbon (10%, 620 mg) was added and the reaction mixture was shaken under H_2 at 48 PSI (3.3 x 10^5 Pa) for 3 days. The reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with 1:1 CH_2Cl_2/acetonitrile and the combined filtrates were concentrated under reduced pressure to give a pink solid. Chromatography (SiO_2, 20-40% CMA/$CHCl_3$) gave a white solid, which was dissolved in methanol and concentrated under reduced pressure (2x) to give (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (265 mg) as an off white solid, mp 262 – 264 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.38 (br s, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 6.99 (dd, J = 2.6, 8.9 Hz, 1H), 6.20 (s, 2H), 5.08 (d, J = 15.5 Hz, 1H), 4.96 (m, 2H), 4.12 (s, 2H), 1.57 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.3, 150.1, 145.2, 138.9, 131.2, 127.8, 127.2, 117.3, 115.3, 104.0, 68.7, 65.1, 50.4, 19.6; MS (ESI) m/z 271 $(M + H)^+$; Anal. calcd for $C_{14}H_{14}N_4O_2 \cdot 0.25\ H_2O \cdot 0.50\ CH_3OH$: C, 59.99; H, 5.56; N, 19.30. Found: C, 60.14; H, 5.86; N, 19.26.

Example 22

3-Bromo-12-methyl-11,12-dihydro-8*H*,10*H*-[1,4]oxazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A suspension of lithium borohydride (26.57 g, 1.220 mol) in ethanol (800 mL) was cooled to approximately 0 °C, and a solution of ethyl 3-aminobutyrate (40.0 g, 0.305 mol) was slowly added. The reaction mixture was heated at reflux for four hours and allowed to cool to room temperature. A solid was present and was removed by filtration and washed with diethyl ether. The filtrate was concentrated under reduced pressure, and the residue was dissolved in diethyl ether. The resulting solution was washed with 10% sodium carbonate, and the aqueous phase was extracted three times with diethyl ether. The combined organic fractions were concentrated under reduced pressure to provide 27.98 g of 3-aminobutan-1-ol containing some starting material.

Part B

Triethylamine (73.5 g, 726 mmol) and the material from Part A were added to a solution of 7-bromo-4-chloro-3-nitroquinoline (34.8 g, 121 mmol, U.S. patent application publication no. US 2004/0147543, Example 1, Parts A through D) in DMF (300 mL), and the reaction mixture was stirred overnight at room temperature. Additional triethylamine (48.97 g, 67.46) and *tert*-butyldimethylsilyl chloride (40.1 g, 266 mmol) were then added, and the reaction was stirred for two hours at room temperature and filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in chloroform. The solution was washed twice with a 2:1 mixture of saturated aqueous sodium bicarbonate and water and three times with 10% aqueous sodium carbonate and then concentrated under reduced pressure. The resulting oil was passed through a plug of basic alumina to provide (7-bromo-3-nitroquinolin-4-yl)-[3-(*tert*-butyldimethylsilanyloxy)-1-methylpropyl]amine.

Part C

A mixture of the material from Part B, acetonitrile (1 L), and 5% platinum on carbon (15.45 g, 79.2 mmol) was placed in a hydrogenation vessel and placed under hydrogen pressure (30 PSI, 2.1 x 10^5 Pa) overnight. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to provide 54.96 g of 7-bromo-N^4-[3-(*tert*-butyldimethylsilanyloxy)-1-methylpropyl]quinoline-3,4-diamine.

Part D

A solution of chloroacetyl chloride (16.1 g, 142 mmol) in chloroform (120 mL) was added dropwise to a solution of 7-bromo-N^4-[3-(*tert*-butyldimethylsilanyloxy)-1-methylpropyl]quinoline-3,4-diamine (54.96 g, 129.5 mmol) in chloroform (500 mL), and the reaction was stirred for three days at room temperature. The solvent was removed under reduced pressure, and the intermediate amide was heated at reflux for two hours in glacial acetic acid (600 mL). The acetic acid was removed under reduced pressure, and the residue was passed through a plug of silica gel (eluting with dichloromethane) to provide 9.53 g of 7-bromo-1-[3-(*tert*-butyldimethylsilanyloxy)-1-methylpropyl]-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinoline and a mixture of three other products. The mixture of products was dissolved in glacial acetic acid and heated at reflux for two days. The acetic acid was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluting with 0% to 5% 2 M methanolic ammonia in dichloromethane) to provide 9.14 g of 3-{2-[(acetyloxy)methyl]-7-bromo-1*H*-imidazo[4,5-*c*]quinolin-1-yl}butyl acetate.

Part E

Lithium hydroxide hydrate (5.3 g, 126 mmol) was added to a solution of 3-{2-[(acetyloxy)methyl]-7-bromo-1*H*-imidazo[4,5-*c*]quinolin-1-yl}butyl acetate (9.14 g, 21.0 mmol) in methanol (150 mL). The resulting mixture was stirred for two days at room temperature and filtered. The methanol was removed from the filtrate under reduced pressure. The crude product mixture was partitioned between dichloromethane and 10% aqueous sodium carbonate. The aqueous fraction was extracted with dichloromethane, and the combined organic fractions were concentrated under reduced pressure. The resulting solid was triturated with acetonitrile, isolated by filtration, and washed with cold acetonitrile to provide 2.13 g of 3-[7-bromo-2-(hydroxymethyl)-1*H*-imidazo[4,5-

c]quinolin-1-yl]butan-1-ol. A portion of this material was mixed with material from a separate run.

Part F

A solution of 3-[7-bromo-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butan-1-ol (3.27 g, 9.34 mmol) in concentrated hydrochloric acid (35 mL) was stirred and heated at 120 °C for three hours and then poured into ice-cold deionized water (80 mL). Aqueous sodium hydroxide (50% w/w) was added to adjust the solution to pH 7, and a precipitate formed. The mixture was extracted with dichloromethane, and the dichloromethane was removed under reduced pressure. The solid residue was triturated with diethyl ether and isolated by filtration to provide 2.62 g of 3-bromo-12-methyl-11,12-dihydro-8*H*,10*H*-[1,4]oxazepino[4',3':1,2]imidazo[4,5-*c*]quinoline.

Part G

MCPBA (4.39 g of 77% purity, 25 mmol) was added to a solution of 3-bromo-12-methyl-11,12-dihydro-8*H*,10*H*-[1,4]oxazepino[4',3':1,2]imidazo[4,5-*c*]quinoline (2.6 g, 7.8 mmol) in chloroform (20 mL), and the reaction mixture was stirred overnight at room temperature. Aqueous ammonium hydroxide was added. The aqueous layer was separated and extracted twice with chloroform. The combined organic fractions were concentrated under reduced pressure and further dried under high vacuum to provide 3-bromo-12-methyl-5-oxido-11,12-dihydro-8*H*,10*H*-[1,4]oxazepino[4',3':1,2]imidazo[4,5-*c*]quinoline.

Part H

Phosphorous(III) oxychloride (1.43 g, 9.36 mmol) was slowly added to a solution of the material from Part G in DMF (20 mL), and the reaction was stirred for ten minutes at room temperature. Saturated aqueous sodium bicarbonate was then added, and the mixture was extracted with dichloromethane. The combined extracts were concentrated under reduced pressure and further dried under high vacuum to provide 3-bromo-6-chloro-12-methyl-11,12-dihydro-8*H*,10*H*-[1,4]oxazepino[4',3':1,2]imidazo[4,5-*c*]quinoline.

Part I

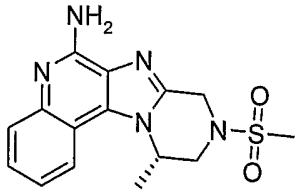
A solution of the material from Part H in 7 N ammonia in methanol (50 mL) was heated overnight in a pressure vessel at 150 °C and allowed to cool. The volatiles were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluting with 4% methanol in dichloromethane) to provide two batches that

were each recrystallized from isopropyl alcohol to provide 0.939 g of 3-bromo-12-methyl-11,12-dihydro-8*H*,10*H*-[1,4]oxazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as off-white needles, mp 247-248 °C.

Anal. Calcd for $C_{15}H_{15}BrN_4O$: C, 51.89; H, 4.35; N, 16.14. Found: C, 51.94; H, 4.36; N, 16.08 (Batch 1). Found: C, 51.88; H, 4.38; N, 16.19 (Batch 2).

Example 23

(11*S*)-11-Methyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

(*S*)-(-)-1,2-Diaminopropane (2.00 g, 13.6 mmol) and 1,8-diaxabicyclo[5.4.0]undec-7-ene (DBU) (4.46 mL, 28.8 mmol) were dissolved in dichloromethane (50 mL) and the solution was cooled to 0 °C under N_2. In another flask, di-*tert*-butyl dicarbonate (2.96 g, 13.6 mmol) was dissolved in dichloromethane (50 mL), and the solution was slowly added to the reaction mixture via cannula. After stirring for 2 hours, the reaction mixture was treated with H_2O (50 mL) and the layers were separated. The organic portion was discarded and the aqueous portion was made basic by the addition of 3 mL of concentrated, aqueous NH_4OH solution and then extracted with CH_2Cl_2 (5 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography (SiO_2, 7% MeOH/$CHCl_3$ saturated with concentrated, aqueous NH4OH solution) afforded *tert*-butyl (2*S*)-2-aminopropylcarbamate (0.50 g) as a colorless liquid.

Part B

A suspension of 3-chloro-4-nitroquinoline (3.04 g, 14.5 mmol) in dichloromethane (150 mL) was treated with triethylamine (4.5 mL, 32.02 mmol) and the reaction mixture was cooled to 0 °C under an atmosphere of N_2. In a separate flask, *tert*-butyl (2*S*)-2-aminopropylcarbamate (2.79 g, 16.0 mmol) was dissolved in dichloromethane (50 mL) and the solution was added into the reaction via cannula. The reaction was allowed to

slowly warm to ambient temperature overnight. The reaction mixture was then washed successively with water (2 x 150 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield *tert*-butyl (2*S*)-2-[(3-nitroquinolin-4-yl)amino]propylcarbamate (5.04 g) as a bright yellow solid.

Part C

tert-Butyl (2*S*)-2-[(3-nitroquinolin-4-yl)amino]propylcarbamate (5.04 g, 14.5 mmol) was dissolved in acetonitrile (300 mL) and the solution was placed in a pressure bottle. Platinum on carbon (5%, 1.03 g) was then added and the reaction mixture was shaken under H_2 at 30 PSI (2.1 x 10^5 Pa). After 20 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with acetonitrile and the combined filtrates were concentrated under reduced pressure to give *tert*-butyl (2*S*)-2-[(3-aminoquinolin-4-yl)amino]propylcarbamate (4.60 g) as an orange foam.

Part D

tert-Butyl (2*S*)-2-[(3-aminoquinolin-4-yl)amino]propylcarbamate (4.60 g, 14.55 mmol) was dissolved in 150 mL of anhydrous 1,2-dichloroethane and the solution was stirred under N_2. Ethyl 2-chloroethanimidoate hydrochloride (3.45 g, 21.8 mmol) was added and the reaction was heated to 60 °C for 24 hours. The reaction mixture was cooled and washed with saturated sodium bicarbonate solution (2 x 100 mL) followed by brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give an orange solid. Chromatography (SiO_2, 60-80% EtOAc/hexanes) gave *tert*-butyl (2*S*)-2-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (2.54 g) as a tan solid.

Part E

tert-Butyl (2*S*)-2-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (2.54 g, 6.77 mmol) was dissolved in 2.2 M HCl in EtOH (50 mL) and the solution was heated to reflux for 15 minutes. N_2 was bubbled through the reaction for 15 minutes, and the remaining volatiles were removed under reduced pressure. The resulting material was partitioned between dichloromethane and water. The organic layer was discarded and the aqueous layer was treated with concentrated NH_4OH solution to adjust to pH 11. The aqueous layer was extracted with dichloromethane (3 x 100 mL), and the combined organic layers were washed with brine. Triethylamine (4 mL) was then added to the solution and it was stirred at ambient temperature overnight. The reaction was washed successively with water (2 x 100 mL) and brine. The organic layer was dried

over Na_2SO_4, filtered, and concentrated to give an orange foam. Chromatography (SiO_2, 20-50% CMA/$CHCl_3$) gave (11*S*)-11-methyl-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline (1.06 g) as an orange foam.

Part F

(11*S*)-11-Methyl-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline (1.06 g, 4.45 mmol) was dissolved in anhydrous dichloromethane (100 mL) under N_2. Triethylamine (1.25 mL, 8.9 mmol) and methanesulfonic anhydride (0.85 g, 4.89 mmol) were sequentially added to the reaction at 0 °C. The reaction was allowed to slowly warm to room temperature overnight. The reaction mixture was then washed successively with water (2 x 100 mL) and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a yellow foam. Chromatography (SiO_2, 10-30% CMA/$CHCl_3$) gave (11*S*)-11-methyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline (1.01 g) as a yellow foam.

Part G

(11*S*)-11-Methyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline (1.01 g, 3.19 mmol) was dissolved in dichloromethane (40 mL) and treated with MCPBA (0.94 g, 77% max). After stirring overnight, the reaction was treated with 20 mL of 2% Na_2CO_3 solution and the layers were separated. The aqueous layer was then extracted with dichloromethane (10 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (11*S*)-11-methyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline 5-oxide (1.06 g) as a tan solid.

Part H

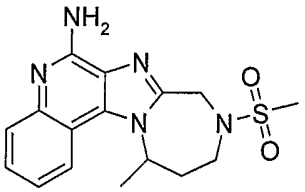
(11*S*)-11-Methyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline 5-oxide (1.06 g, 3.19 mmol) was dissolved in dichloromethane (100 mL) and treated with concentrated ammonium hydroxide solution (10 mL). The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (610 mg, 3.19 mmol) was carefully added. Rapid stirring was continued overnight. The reaction mixture was then diluted with 25 mL of CH_2Cl_2 and 25 mL of H_2O. The layers were separated and the organic portion was washed successively with aqueous saturated sodium bicarbonate solution (2 x 50 mL), H_2O and brine. The organic

portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 20-40% CMA/$CHCl_3$) gave (11*S*)-11-methyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-c]quinolin-6-amine (520 mg) as a white solid, mp 258 – 261 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.03 (d, J = 7.4 Hz, 1H), 7.64 (dd, J = 1.1, 8.3 Hz, 1H), 7.45 (m, 1H), 7.29 (m, 1H), 6.62 (s, 2H), 5.32 (m, 1H), 4.78 (m, 1H), 4.59 (d, J = 15.6 Hz, 1H), 3.87 (d, J = 12.8 Hz, 1H), 3.64 (dd, J = 12.8, 3.3 Hz, 1H), 3.16 (s, 3H), 1.55 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.1, 145.2, 143.9, 131.6, 127.1, 127.0, 126.7, 121.7, 120.7, 114.8, 50.6, 48.4, 45.2, 35.9, 19.5; MS (ESI) *m/z* 332 $(M + H)^+$; Anal. calcd for $C_{15}H_{17}N_5O_2S$: C, 54.37; H, 5.17; N, 21.13. Found: C, 54.13; H, 4.99; N, 21.20.

Example 24

12-Methyl-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine formic acid salt



Part A

Triethylamine (12.8 mL, 91.8 mmol) was added to a solution of 4-chloro-3-nitroquinoline (8.0 g, 38 mmol) in DMF (100 mL). The resulting solution was stirred for five minutes at room temperature, and then ethyl 3-aminobutyrate (6.2 mL, 42 mmol) was added. The reaction was stirred overnight at room temperature and poured into deionized water (320 mL). The mixture was extracted with ethyl acetate (1 x 125 mL and 2 x 100 mL). The combined extracts were washed with brine (3 x 120 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter agent, concentrated under reduced pressure, and further dried under high vacuum to provide 11.5 g of ethyl 3-[(3-nitroquinolin-4-yl)amino]butanoate as a yellow solid.

Part B

A Parr vessel was charged with a solution of ethyl 3-[(3-nitroquinolin-4-yl)amino]butanoate (11.5 g, 37.9 mmol) in acetonitrile (150 mL) followed by 5% platinum on carbon (1.2 g). The mixture was placed under hydrogen pressure overnight and then

filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure and further dried under high vacuum to provide 10.5 g of ethyl 3-[(3-aminoquinolin-4-yl)amino]butanoate as a sticky, yellow solid.

Part C

Ethyl 2-chloroethanimidoate hydrochloride (10.8 g, 68.4 mmol) was added to a solution of ethyl 3-[(3-aminoquinolin-4-yl)amino]butanoate (9.41 g, 34.4 mmol) in chloroform (130 mL), and the reaction was stirred at room temperature for three days and then heated at reflux for two hours. An analysis by liquid chromatography/mass spectrometry (LC/MS) indicated the presence of starting material, and additional ethyl 2-chloroethanimidoate hydrochloride (2.7 g) was added. The reaction was heated at reflux for an additional 1.5 hours, allowed to cool to room temperature, diluted with chloroform (100 mL), washed sequentially with brine (2 x 150 mL) and deionized water (100 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter agent, concentrated under reduced pressure, and further dried overnight under high vacuum to provide 11.15 g of ethyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate as a dark yellow solid.

Part D

A solution of ethyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate (8.22 g, 24.8 mmol) in 7 N ammonia in methanol (140 mL) was stirred overnight at room temperature. The volatiles were removed under reduced pressure, and the residue was further dried under high vacuum and purified by automated flash chromatography (eluting with a gradient of dichloromethane/methanol/concentrated ammonium hydroxide in a gradient from 100:0:0 to 50:47.5:2.5) to provide 12-methyl-8,9,11,12-tetrahydro-10*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-10-one as an orange solid. Automated flash chromatography was carried out using a combination of a COMBIFLASH system (an automated high-performance flash purification product available from Teledyne Isco, Inc., Lincoln, Nebraska, USA) and a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA).

Part E

MCPBA (2.73 g of 77% purity, 16 mmol) was added to a solution of 12-methyl-8,9,11,12-tetrahydro-10*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-10-one (1.3 g,

4.9 mmol) in chloroform (20 mL), and the reaction mixture was stirred for 15 minutes at room temperature. Concentrated ammonium hydroxide (30 mL) and *p*-toluenesulfonyl chloride (1.12 g, 5.86 mmol) were sequentially added, and the resulting mixture was stirred at room temperature for two hours. An analysis by LC/MS indicated the presence of the 5*N*-oxide, and additional *p*-toluenesulfonyl chloride (1 equivalent) was added. The mixture was stirred at room temperature overnight. The organic layer was separated and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 0% to 15% 2 N methanolic ammonia in chloroform over a period of 42 minutes) followed by recrystallization from acetonitrile to provide 389 mg of 6-amino-12-methyl-8,9,11,12-tetrahydro-10*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-10-one.

Part F

Borane THF complex (2.76 mL of a 1 M solution in THF) was added to a solution of 6-amino-12-methyl-8,9,11,12-tetrahydro-10*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-10-one (0.389 g, 1.38 mmol) in THF (5 mL), and the mixture was stirred at room temperature overnight and then heated at reflux for six hours. An analysis by LC/MS indicated the reaction was incomplete, and additional borane tetrahydrofuran complex (2.76 mL) was added. The reaction mixture was heated at reflux overnight, allowed to cool, and concentrated under reduced pressure. The residue was treated with chloroform, and a solid was present that was isolated by filtration to provide 12-methyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as a yellow solid.

Part G

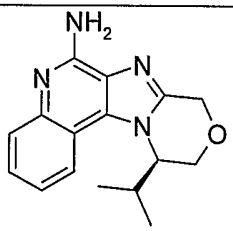
Triethylamine (1.4 g, 14 mmol) and methanesulfonyl chloride (189.7 mg, 1.656 mmol) were sequentially added to the material from Part F in DMF (15 mL), and the reaction was stirred at room temperature for one hour. An analysis by LC/MS showed no reaction had taken place, and additional methanesulfonyl chloride (1 equivalent) was added. After the reaction was stirred for an additional hour, an analysis by LC/MS indicated the presence of starting material, and additional methanesulfonyl chloride (2 equivalents) was added. The reaction mixture was stirred for another hour and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluting with 0% to 25% 2 N methanolic

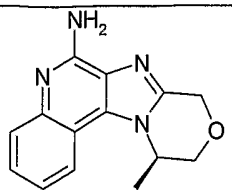
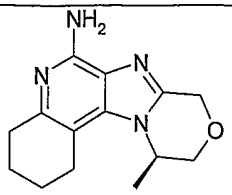
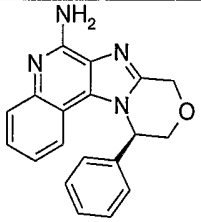
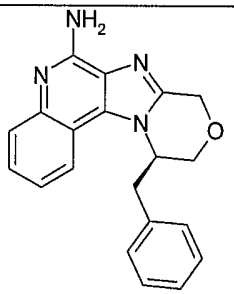
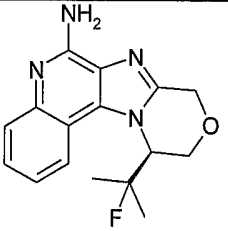
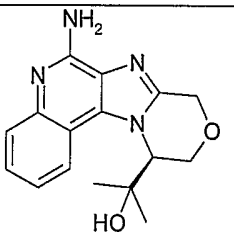
ammonia in chloroform over a period of 42 minutes). The fractions containing product were combined and concentrated under reduced pressure, and the resulting product mixture was boiled in trifluoroacetic anhydride and then concentrated under reduced pressure. The residue was treated with aqueous sodium hydroxide and purified by reversed phase preparative HPLC (eluting with 5% to 30% solvent B in three minutes and 30% to 95% solvent B in seven minutes wherein solvent B is 0.5% formic acid in acetonitrile and solvent A is 0.5% formic acid in water) using a HPLC purification system obtained from Shimadzu corporation (based in Kyoto, Japan) to provide 48 mg of 12-methyl-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine formic acid salt.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17-8.15 (m, 1H), 7.64 (d, *J*= 8.0 Hz, 1H), 7.46 (t, *J*= 7.5 Hz, 1H), 7.28 (t, *J*= 7.2 Hz, 1H), 6.80 (s, 2H), 5.56-5.52 (m, 1H), 4.80 (q, *J*= 14.1 Hz, 2H), 3.81-3.57 (m, 4H), 2.65 (s, 3H), 1.64 (d, *J*= 6.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9, 153.9, 152.2, 145.9, 129.6, 128.0, 127.6, 124.3, 123.0, 116.8, 54.0, 47.6, 46.1, 39.0, 33.1, 20.3; HRMS cald. for $C_{16}H_{19}N_5O_2S$: 346.1338. Found: 346.1340.

Examples 25 - 31

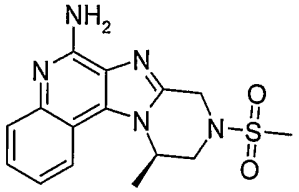
The following examples are enantiomers of the compounds prepared in Examples 1, 5, 6, 9, 10, 11, and 13, and they were prepared according to the methods indicated in the table below using the amino alcohol listed in the table below instead of its enantiomer. In addition to the method and the amino alcohol used for the synthesis, the table provides the structure of the example obtained and its characterization data.

Ex.	Method of	Amino alcohol	structure	mp (°C)	Anal.
25	Ex. 1	(2*R*)-2-Amino-3-methylbutan-1-ol		248-249	Calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 67.86; H, 6.50; N, 19.89.

26	Ex. 5	(*R*)-2-amino-1-propanol		280-282	Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.13; H, 5.53; N, 22.25.
27	Ex. 6	Not applicable[a]		209-211	Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.01; H, 7.01; N, 21.64.
28	Ex. 9	(2*R*)-2-amino-2-phenylethanol		284-286	Calcd for $C_{19}H_{16}N_4O$: C, 72.14; H, 5.10; N, 17.71. Found: C, 71.80; H, 4.96; N, 17.56.
29	Ex. 10	(2*R*)-2-amino-3-phenylpropan-1-ol		170-177	Calcd for $C_{20}H_{18}N_4O \cdot 0.25\ H_2O$: C, 71.73; H, 5.57; N, 16.73. Found: C, 71.92; H, 5.60; N, 16.79.
30	Ex. 11	(2*S*)-2-amino-3-fluoro-3-methylbutan-1-ol		242-244	Calcd for $C_{16}H_{17}FN_4O$: C, 63.99; H, 5.71; N, 18.65. Found: C, 63.78; H, 5.51; N, 18.52.
31	Ex. 13	(2*S*)-2-amino-3-methylbutane-1,3-diol hydrochloride		218-219	Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.09; H, 6.26; N, 18.60.

Example 32

(11*R*)-11-Methyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine

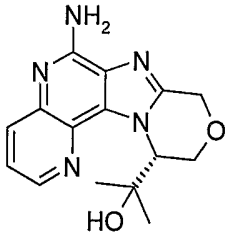


The methods described in Parts A through H of Example 23 were followed using (*R*)-(+)-1,2-diaminopropane instead of (*S*)-(-)-1,2-diaminopropane in Part A to provide the title compound as off-white needles, mp 258 – 261 °C.

Anal. calcd for $C_{15}H_{17}N_5O_2S$: C, 54.37; H, 5.17; N, 21.13. Found: C, 53.99; H, 5.16; N, 21.15.

Example 33

2-[(11*R*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]-1,5-naphthyridin-11-yl]propan-2-ol



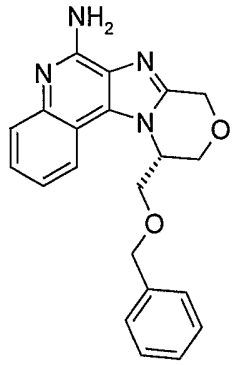
The title compound was prepared from (1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylpropylamine and 4-chloro-3-nitro[1,5]naphthyridine following Parts C through I listed for the preparation of Example 13 with the modification that Part H was carried out in $CHCl_3$ as the solvent. Chromatography of the final compound (SiO_2, 0-20% CMA/$CHCl_3$) afforded 2-[(11*R*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]-1,5-naphthyridin-11-yl]propan-2-ol as an off white solid, mp 242 – 246 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (dd, J = 1.5, 4.4 Hz, 1H), 7.98 (dd, J = 1.5, 8.4 Hz, 1H), 7.48 (m, 1H), 6.95 (s, 2H), 6.05 (s, 1H), 5.18 (m, 2H), 5.00 (d, J = 16.3 Hz, 1H), 4.43 (d, J = 12.6 Hz, 1H), 4.00 (dd, J = 3.2, 12.6 Hz, 1H), 1.40 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.7, 147.9, 142.6, 140.4, 133.9, 132.7, 129.8, 122.5, 73.4, 64.9,

64.2, 62.0, 29.2, 26.5; MS (ESI) *m/z* 300 $(M + H)^+$. Anal. calcd for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 59.93; H, 5.59; N, 23.35.

Example 34

(11*S*)-11-[(Benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Methyl *N*-trityl-L-serinate (3.61 g, 10.0 mmol), prepared by the method of Baldwin, *Tetrahedron*, 49, pp. 6309-6330, (1993), was dissolved in 50 mL of CH_2Cl_2 followed by the addition of 25 mL of 50% aqueous NaOH solution. To the stirred mixture were added benzyltrimethylammonium chloride (186 mg, 1.00 mmol) and benzyl bromide (1.20 mL, 10.0 mmol). After stirring overnight, the mixture was treated with 100 mL of ice water. After all of the ice had melted, 100 mL of CH_2Cl_2 was added and the layers were separated. The aqueous portion was extracted with another 50 mL of CH_2Cl_2 and the combined organic layers were washed with H_2O (2 x 100 mL) and brine (3 x 50 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated. Chromatography (SiO_2, 10-20% ethyl acetate/hexanes) gave 3.22 g of methyl *O*-benzyl-*N*-trityl-L-serinate as a colorless syrup.

Part B

Methyl *O*-benzyl-*N*-trityl-L-serinate (2.94 g, 6.52 mmol) was dissolved in 100 mL of anhydrous Et_2O and the solution was cooled to 0 °C under N_2. Lithium aluminum hydride (1.63 g, 42.9 mmol) was added and the mixture was stirred for 90 minutes. The reaction mixture was then sequentially treated with 1.63 mL of H_2O, 1.63 mL of 15% NaOH solution and 4.90 mL of H_2O. After stirring for 30 minutes, the reaction mixture was filtered to remove the white solid. The solid was washed with several portions of Et_2O

and the combined filtrates were concentrated under reduced pressure. Chromatography (SiO_2, 15-20% ethyl acetate/hexanes) gave 2.78 g of (2*R*)-3-(benzyloxy)-2-(tritylamino)propan-1-ol as a colorless oil.

Part C

A solution of (2*R*)-3-(benzyloxy)-2-(tritylamino)propan-1-ol (2.68 g, 6.34 mmol) dissolved in 100 mL of CH_2Cl_2 was treated with triethylamine (1.00 mL, 7.19 mmol), *tert*-butyldimethylsilyl chloride (1.08 g, 7.15 mmol) and DMAP (79 mg, 0.65 mmol) and the reaction mixture was stirred under N_2 overnight. The reaction mixture was then concentrated and the resulting material was dissolved in 50 mL of CH_2Cl_2 and washed with H_2O and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 10% ethyl acetate/hexanes) gave 3.03 g of (2*S*)-1-(benzyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-tritylpropan-2-amine as a colorless syrup.

Part D

(2*S*)-1-(Benzyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-tritylpropan-2-amine (3.02 g, 5.62 mmol) was dissolved in 60 mL of anhydrous CH_2Cl_2 and 9.1 mL of glacial acetic acid. The reaction mixture was cooled to 0 °C under an atmosphere of N_2 and boron trifluoride diethyl etherate (0.75 mL, 5.92 mmol) was added dropwise over several minutes. After stirring for 5 hours, the reaction mixture was treated with 85 mL of cold, aqueous 10% NaOH solution. The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 0-5% methanol/$CHCl_3$) gave 1.57 g of (2*S*)-1-(benzyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy}propan-2-amine as a white solid.

Part E

(2*S*)-1-(Benzyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy}propan-2-amine (1.55 g, 5.25 mmol) was dissolved in 60 mL of dry CH_2Cl_2. Triethylamine (1.46 mL, 10.5 mmol) and 4-chloro-3-nitroquinoline (1.09 g, 5.25 mmol) were then added and the reaction was stirred under N_2 for 2 days. The reaction mixture was then concentrated and the resulting material was partitioned between 50 mL of CH_2Cl_2 and 50 mL of saturated $NaHCO_3$ solution. The layers were separated and the organic portion was washed with H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced

pressure. Chromatography (SiO_2, 0-10% ethyl acetate/ CH_2Cl_2) gave 1.81 g of *N*-[(1*S*)-2-(benzyloxy)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)ethyl]-3-nitroquinolin-4-amine as a yellow solid.

Part F

N-[(1*S*)-2-(Benzyloxy)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)ethyl]-3-nitroquinolin-4-amine (1.81 g, 3.88 mmol) was dissolved in 30 mL of acetonitrile and the solution was placed in a pressure bottle. Platinum on carbon (5%, 180 mg) was then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa). After 5.5 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with acetonitrile and the combined filtrates were concentrated under reduced pressure to give 1.66 g of N^4-[(1*S*)-2-(benzyloxy)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)ethyl]quinoline-3,4-diamine as an orange solid.

Part G

N^4-[(1*S*)-2-(Benzyloxy)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)ethyl]quinoline-3,4-diamine (1.66 g, 3.80 mmol) was dissolved in 40 mL of anhydrous 1,2-dichloroethane and the solution was stirred under N_2. Ethyl 2-chloroethanimidoate hydrochloride (1.80 g, 11.4 mmol) was then added and the reaction mixture was heated to 70 °C. After stirring overnight, the reaction mixture was cooled and treated with 20 mL of saturated $NaHCO_3$ solution. The layers were separated and the organic portion was washed successively with H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 20-50% ethyl acetate/hexanes) gave 1.61 g of 1-[(1*S*)-2-(benzyloxy)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)ethyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline as a golden syrup.

Part H

1-[(1*S*)-2-(Benzyloxy)-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)ethyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (1.61 g, 3.13 mmol) was dissolved in 250 mL of anhydrous CH_2Cl_2 and the solution was cooled to -78 °C under N_2. A 1.0 M solution of tetrabutylammonium fluoride in THF (3.43 mL, 3.43 mmol) was added and the stirred solution was allowed to warm to ambient temperature overnight. The reaction mixture was then washed successively with 50 mL of saturated $NaHCO_3$ solution and brine (4 x 50 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 0-3% methanol/$CHCl_3$) gave 0.92 g of (11*S*)-11-

[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as a colorless syrup.

Part I

(11*S*)-11-[(Benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (0.92 g, 2.67 mmol) was dissolved in 25 mL of CH_2Cl_2 and treated with MCPBA (0.81 g, 57-86% purity). After stirring for 2 hours, the reaction mixture was treated with 25 mL of CH_2Cl_2 and 25 mL of 5% Na_2CO_3 solution and the layers were separated. The aqueous portion was extracted with an additional 10 mL of CH_2Cl_2. The combined organic layers were washed successively with H_2O (20 mL) and brine (20 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 0.96 g of (11*S*)-11-[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide as a light-brown solid.

Part J

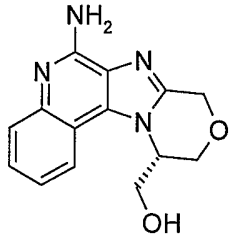
(11*S*)-11-[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (0.96 g, 2.67 mmol) was dissolved in 25 mL of CH_2Cl_2 and treated with 2.5 mL of concentrated aqueous NH_4OH solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (0.51 g, 2.67 mmol) was carefully added. Rapid stirring was continued for 2.5 hours. The reaction mixture was then treated with 50 mL of CH_2Cl_2 and 25 mL of H_2O. The layers were separated and the organic portion was washed successively with 5% Na_2CO_3 solution (3 x 25 mL), H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 15-25% CMA/$CHCl_3$) gave a light-brown foam. Crystallization from ethyl acetate and a small amount of methanol gave (11*S*)-11-[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (420 mg) fine white needles, mp 184.6-186.2 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, J = 7.4 Hz, 1H), 7.61 (dd, J = 1.0, 8.4 Hz, 1H), 7.42 (m, 1H), 7.34-7.28 (m, 5H), 7.23 (m, 1H), 6.59 (s, 2H), 5.09 (d, J = 15.7 Hz, 1H), 5.09 (m, 1H), 4.97 (d, J = 15.7 Hz, 1H), 4.61 (d, J = 12.3 Hz, 1H), 4.55 (d, J = 12.3 Hz, 1H), 4.38 (d, J = 12.1 Hz, 1H), 4.10 (dd, J = 2.4, 12.1 Hz, 1H), 3.86-3.76 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.7, 145.2, 144.6, 137.7, 131.5, 128.2, 127.5, 127.4, 126.5, 126.2, 126.1, 121.1, 120.0, 114.3, 72.3, 67.8, 64.5, 64.1, 53.3; MS (ESI) *m/z* 361

$(M + H)^+$. Anal. calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55. Found: C, 69.65; H, 5.48; N, 15.52.

Example 35

[(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methanol

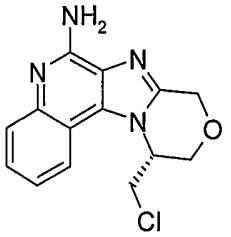


(11*S*)-11-[(Benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (297 mg, 0.825 mmol) was dissolved in 20 mL of methanol and the solution was placed in a pressure bottle. Palladium on carbon (10%, 230 mg) and 0.5 mL of 3 M HCl in ethanol were then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa). After 18 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in H_2O and the solution was made basic by the addition of concentrated aqueous NH_4OH solution. The aqueous solution was extracted with 10% $MeOH/CH_2Cl_2$ several times and the combined organic layers were concentrated under reduced pressure. Chromatography (SiO_2, 25-75% $CMA/CHCl_3$) gave a white powder. Crystallization from ethyl acetate gave 85 mg of the title compound as white, fluffy crystals, mp 238.6-239.8 °C.

^1H NMR (300 MHz, DMSO-d_6) δ 8.04 (d, J = 7.4 Hz, 1H), 7.63 (dd, J = 1.0, 8.3 Hz, 1H), 7.45 (m, 1H), 7.27 (m, 1H), 6.57 (s, 2H), 5.50 (dd, J = 5.0, 6.6 Hz, 1H), 5.08 (d, J = 15.7 Hz, 1H), 4.96 (d, J = 15.7 Hz, 1H), 4.83 (m, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.05 (dd, J = 2.0, 12.1 Hz, 1H), 3.86-3.69 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.7, 145.2, 144.6, 131.6, 126.5, 126.2, 126.1, 121.1, 120.2, 114.4, 64.6, 63.3, 59.5, 55.4; MS (ESI) *m/z* 271 $(M + H)^+$. Anal. calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.98; H, 5.01; N, 20.73.

Example 36

(11*R*)-11-(Chloromethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

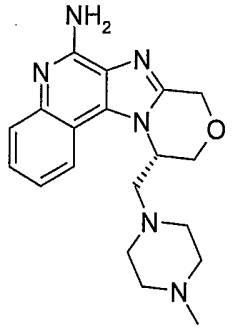


Thionyl chloride (1.5 mL, 20.7 mmol) was added neat to [(11*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methanol (280 mg, 1.03 mmol). The nearly homogeneous yellow reaction mixture was heated to 70 °C for 2 hours and turned dark red. The reaction mixture was cooled to ambient temperature and poured over ice. While maintaining the temperature at 0 °C, the pH of the mixture was brought to 14 by addition of 50% aqueous NaOH. The resulting white suspension was extracted with $CHCl_3$. The layers were separated and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide a tan foam. The tan foam was slurried with acetonitrile and filtered to provide 185 mg of the desired product as a white solid, mp 230-232 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (dd, J = 1.1, 8.3 Hz, 1H), 7.64 (dd, J = 1.0, 8.4 Hz, 1H), 7.46 (ddd, J = 1.4, 7.0, 8.4 Hz, 1H), 7.31 (ddd, J = 1.4, 7.0, 8.1 Hz, 1H), 6.63 (s, 2H), 5.27 (dt, J = 2.9, 9.4 Hz, 1H), 5.12 (d, J = 16 Hz, 1H), 5.00 (d, J = 16 Hz, 1H), 4.42 (d, J = 13 Hz, 1H), 4.16 (br d, J = 12 Hz, 1H), 4.07-3.93 (m, 2H), ; ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.7, 145.0, 144.7, 131.3, 126.7, 126.31, 126.28, 121.3, 119.6, 114.2, 64.7, 63.7, 54.5, 42.1; MS (APCI) *m/z* 289 $(M + H)^+$. Anal. calcd for $C_{14}H_{13}ClN_4O$: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.06; H, 4.31; N, 19.57.

Example 37

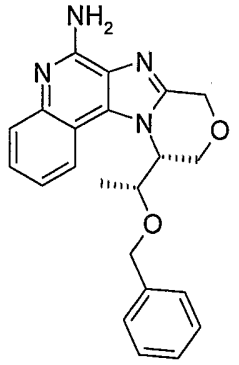
(11*S*)-11-[(4-Methylpiperazin-1-yl)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Methyl piperazine (0.3 mL, 2.5 mmol) was added to a vial containing (11*R*)-11-(chloromethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (90 mg, 0.31 mmol). The vial was placed in a stainless-steel, high-pressure vessel and heated to 150 °C for 18 hours. The reaction mixture was cooled to ambient temperature. The resulting light brown oil was purified by chromatography (SiO_2, 0-30% CMA/$CHCl_3$). The resulting oil was slurried in acetonitrile to produce a solid which was isolated by filtration to give 18 mg of the desired product as a tan solid, mp 187-190 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.01 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 7.2, 8.4 Hz, 1H), 7.31 (dd, J = 7.0, 8.3 Hz, 1H), 6.66 (s, 2H), 5.16 (m, 1H), 5.10 (d, J = 16 Hz, 1H), 5.00 (d, J = 16 Hz, 1H), 4.46 (d, J = 12 Hz, 1H), 4.02 (br d, J = 12 Hz, 1H), 3.34-2.50 (m, 10H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.6, 145.4, 144.1, 131.4, 126.7, 126.2, 125.8, 121.1, 120.3, 114.2, 64.5, 64.1, 57.0, 54.1, 52.1, 51.8, 44.7; MS (APCI) *m/z* 353 $(M + H)^+$. Anal. calcd for $C_{19}H_{24}N_6O \cdot 1.4\ H_2O$: C, 60.43; H, 7.15; N, 22.25. Found: C, 60.25; H, 7.09; N, 22.33.

Example 38

(11*R*)-11-[(1*R*)-1-(benzyloxy)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Methyl L-threoninate hydrochloride (16.9 g, 100 mmol), prepared by the method of Lall, *J. Org. Chem.*, 67, pp. 1536-1547, was dissolved in 200 mL of anhydrous CH_2Cl_2 and the solution was cooled to 0 °C under N_2. Triethylamine (27.8 mL, 200 mmol) was then added followed by triphenylmethylchloride (27.9 g, 100 mmol) and the reaction was stirred and allowed to warm to ambient temperature overnight. The reaction mixture was then filtered and the resulting solid was rinsed with several portions of CH_2Cl_2. The combined filtrates were concentrated under reduced pressure and the resulting syrup was dissolved in 150 mL of ethyl acetate and then washed successively with 100 mL of saturated aqueous $NaHCO_3$ solution, 100 mL of 10% aqueous citric acid solution, 50 mL of H_2O and 50 mL of brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a syrup. The syrup was treated with 200 mL of hexanes and the mixture was stirred rapidly overnight to give a white solid. The solvent was decanted and the solid was washed with an additional portion of hexanes. The mixture was filtered and the isolated white solid was dried under vacuum for several days to give methyl *N*-trityl-L-threoninate (32.4 g) as a sticky, white powder.

Part B

A 250-mL, round-bottomed flask, under an atmosphere of N_2, was charged with sodium hydride (60% oil dispersion, 772 mg, 19.3 mmol). The sodium hydride was washed with 3 portions of hexanes to remove the oil and then 8 mL of anhydrous DMF was added followed by benzyl bromide (3.38 mL, 28.4 mmol). The solution was cooled to 0 °C and then a solution of methyl *N*-trityl-L-threoninate (4.83 g, 12.9 mmol) dissolved in

12 mL of DMF was added dropwise via cannula over 5 minutes. After stirring for 2 hours, the reaction mixture was treated with saturated aqueous Na_2CO_3 solution and 200 mL of Et_2O and the layers were separated. The organic portion was washed successively with H_2O (5 x 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 5-10% ethyl acetate/hexanes) gave 4.61 g of methyl *O*-benzyl-*N*-trityl-L-threoninate as a colorless syrup.

Part C

Methyl *O*-benzyl-*N*-trityl-L-threoninate (4.61 g, 9.91 mmol) was dissolved in 100 mL of anhydrous Et_2O and the solution was cooled to 0 °C under N_2. Lithium aluminum hydride (2.28 g, 60 mmol) was added and the mixture was stirred for 2 hours. The reaction mixture was then sequentially treated with 2.28 mL of H_2O, 2.28 mL of 15% NaOH solution and 6.84 mL of H_2O. After stirring for 30 minutes, the reaction mixture was filtered to remove the white solid. The solid was washed with several portions of Et_2O and the combined filtrates were concentrated under reduced pressure. Chromatography (SiO_2, 10-20% ethyl acetate/hexanes) gave 4.34 g of (2*R*,3*R*)-3-(benzyloxy)-2-(tritylamino)butan-1-ol as a colorless syrup.

Part D

A solution of (2*R*,3*R*)-3-(benzyloxy)-2-(tritylamino)butan-1-ol (4.33 g, 9.91 mmol) dissolved in 150 mL of CH_2Cl_2 was treated with triethylamine (1.52 mL, 10.9 mmol), *tert*-butyldimethylsilyl chloride (1.65 g, 10.9 mmol) and DMAP (122 mg, 1.00 mmol) and the reaction mixture was stirred under N_2 overnight. The reaction mixture was then concentrated and the resulting material was dissolved in 50 mL of CH_2Cl_2 and washed successively with H_2O and brine. The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 5-10% ethyl acetate/hexanes) gave 3.26 g of (2*R*,3*R*)-3-(benzyloxy)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-tritylbutan-2-amine as a white solid.

Part E

(2*R*,3*R*)-3-(benzyloxy)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-tritylbutan-2-amine (3.26 g, 5.92 mmol) was dissolved in 75 mL of anhydrous CH_2Cl_2 and 9.6 mL of glacial acetic acid. The reaction mixture was cooled to 0 °C under an atmosphere of N_2 and boron trifluoride diethyl etherate (790 µL, 5.92 mmol) was added dropwise over several minutes. After stirring for 4 hours, the reaction mixture was treated with 90 mL of cold, aqueous

10% NaOH solution. The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 0-5% methanol/$CHCl_3$) gave 1.83 g of (2*R*,3*R*)-3-(benzyloxy)-1-{[*tert*-butyl(dimethyl)silyl]oxy}butan-2-amine as a white solid.

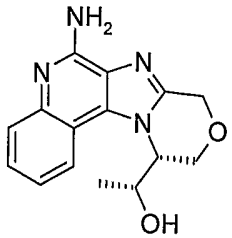
Part F

The title compound was prepared from 4-chloro-3-nitroquinoline and (2*R*,3*R*)-3-(benzyloxy)-1-{[*tert*-butyl(dimethyl)silyl]oxy}butan-2-amine following Parts E through J listed for the preparation of Example 34. Chromatography (SiO_2, 10-40% CMA/$CHCl_3$) gave a light-orange foam. Crystallization from ethyl acetate gave (11*R*)-11-[(1*R*)-1-(benzyloxy)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as an off-white solid, mp 189.0 - 190.8 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, J = 7.5 Hz, 1H), 7.59 (dd, J = 1.0, 8.4 Hz, 1H), 7.38 (m, 1H), 7.24-7.22 (m, 3H), 7.12-7.06 (m, 3H), 6.58 (s, 2H), 5.07 (d, J = 15.7 Hz, 1H), 5.05 (m, 1H), 4.97 (d, J = 15.7 Hz, 1H), 4.55 (d, J = 12.4 Hz, 1H), 4.48 (d, J = 12.5 Hz, 1H), 4.36 (d, J = 12.4 Hz, 1H), 4.14-4.04 (m, 2H), 1.13 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.7, 145.2, 144.7, 138.0, 132.2, 128.0, 127.3, 127.2, 126.3, 125.9, 120.8, 120.7, 114.8, 73.5, 70.1, 64.0, 63.6, 56.5, 15.4; MS (ESI) *m/z* 375 $(M + H)^+$. Anal. calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.55; H, 5.77; N, 15.15.

Example 39

(1*R*)-1-[(11*R*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]ethanol



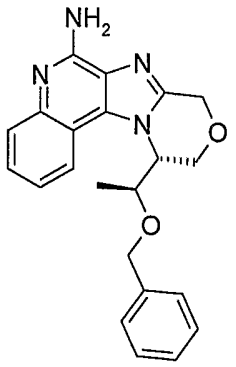
(11*R*)-11-[(1*R*)-1-(Benzyloxy)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (512 mg, 1.37 mmol) was dissolved in 30 mL of methanol and the solution was placed in a pressure bottle. Palladium on

carbon (10%, 200 mg) and 2.5 mL of 3 M HCl in ethanol were then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4 x 10^5 Pa). After 24 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in H_2O and the solution was made basic by the addition of concentrated aqueous NH_4OH solution. The aqueous solution [redacted] 10% $MeOH/CHCl_3$ several times and the combined organic layers were concentrated under reduced pressure. Chromatography (SiO_2, 25-50% CMA/$CHCl_3$) gave an off-white powder. Crystallization from ethyl acetate and methanol gave 353 mg of the title compound as white needles, mp 215.3 - 218.6 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (d, J = 7.4 Hz, 1H), 7.61 (dd, J = 1.0, 8.3 Hz, 1H), 7.42 (ddd, J = 1.3, 7.0, 8.3 Hz, 1H), 7.24 (ddd, J = 1.2, 7.1, 8.1 Hz, 1H), 6.57 (s, 2H), 5.41 (d, J = 4.4 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 4.93 (d, J = 15.6 Hz, 1H), 4.80 (m, 1H), 4.53 (d, J = 12.4 Hz, 1H), 4.32 (m, 1H), 4.05 (dd, J = 3.3, 12.4 Hz, 1H), 1.02 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.8, 145.3, 144.6, 132.1, 126.4, 126.3, 126.0, 120.8, 120.2, 114.8, 65.9, 64.0, 62.8, 57.9, 18.3; MS (ESI) m/z 285 $(M + H)^+$. Anal. calcd for $C_{15}H_{16}N_4O_2 \cdot 0.5\ H_2O$: C, 61.42; H, 5.84; N, 19.10. Found: C, 61.30; H, 5.58; N, 19.07.

Example 40

(11*R*)-11-[(1*S*)-1-(benzyloxy)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A 500-mL, round-bottomed flask was charged with methyl *N*-trityl-L-threoninate (3.75 g, 10.0 mmol), benzoic acid (2.44 g, 20.0 mmol) and triphenylphosphine (5.24 g,

20.0 mmol). Anhydrous THF (50 mL) was added and the solution was cooled to 0 °C under N_2 with stirring. A 40% solution of diethylazodicarboxylate in toluene (9.06 mL, 20.0 mmol) was added dropwise and the reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was treated with 50 mL of ethyl acetate and 50 mL of saturated aqueous $NaHCO_3$ solution. The layers were separated and the organic portion was washed successively with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow syrup. The yellow syrup was dissolved in 25 mL of Et_2O and then treated with hexanes until a white precipitate formed. The solid was removed by filtration and the filtrate was concentrated to give a yellow oil. Chromatography (SiO_2, 33-100% CH_2Cl_2/hexanes) gave 1.24 g of methyl *O*-benzoyl-*N*-trityl-L-allothreoninate as a colorless solid.

Part B

A solution of the methyl *O*-benzoyl-*N*-trityl-L-allothreoninate (1.24 g, 2.59 mmol) dissolved in 15 mL of anhydrous methanol was treated with 0.1 mL of a 25% solution of sodium methoxide in methanol. The reaction mixture was stirred under N_2 for 2 days. The reaction was then treated with 10 mL of saturated aqueous $NaHCO_3$ solution and the methanol was removed under reduced pressure. The reaction mixture was then treated with 30 mL of ethyl acetate and washed successively with H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a colorless solid. Crystallization from ethyl acetate and hexanes gave methyl *N*-trityl-L-allothreoninate (0.60 g) as colorless crystals.

Part C

(2*R*,3*S*)-3-(Benzyloxy)-1-{[*tert*-butyl(dimethyl)silyl]oxy}butan-2-amine was prepared from methyl *N*-trityl-L-allothreoninate following Parts B through E listed for the preparation of Example 38. The product was obtained as colorless syrup.

Part D

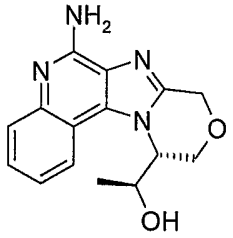
The title compound was prepared from (2*R*,3*S*)-3-(benzyloxy)-1-{[*tert*-butyl(dimethyl)silyl]oxy}butan-2-amine and 4-chloro-3-nitroquinoline and (2*R*,3*S*)-3-(benzyloxy)-1-{[*tert*-butyl(dimethyl)silyl]oxy}butan-2-amine following Parts E through J listed for the preparation of Example 34. Chromatography (SiO_2, 10-30% CMA/$CHCl_3$) gave a light-orange foam. Crystallization from acetonitrile gave (11*R*)-11-[(1*S*)-1-

(benzyloxy)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as white, fluffy crystals, mp 86.6-89.7 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, J = 7.5 Hz, 1H), 7.60 (dd, J = 1.0, 8.3 Hz, 1H), 7.39 (m, 1H), 7.20-7.10 (m, 4H), 7.01-6.95 (m, 2H), 6.58 (s, 2H), 5.11 (d, J = 1.9 Hz, 1H), 5.04 (d, J = 15.6 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 4.43 (dd, J = 1.6, 12.2 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.22-4.12 (m, 2H), 4.09 (d, J = 12.0 Hz, 1H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.7, 145.3, 143.6, 136.9, 130.8, 126.8, 126.1, 126.0, 125.3, 125.0, 119.7, 119.6, 113.7, 73.6, 69.2, 63.0, 62.8, 56.2, 14.9; MS (ESI) *m/z* 375 $(M + H)^+$. Anal. calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.40; H, 5.91; N, 15.01.

Example 41

(1*S*)-1-[(11*R*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]ethanol

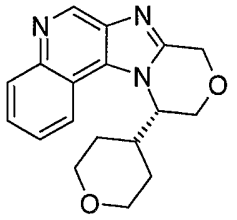


(11*R*)-11-[(1*S*)-1-(Benzyloxy)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (512 mg, 1.37 mmol) was dissolved in 30 mL of methanol and the solution was placed in a pressure bottle. Palladium on carbon (10%, 200 mg) and 2.5 mL of 3 M HCl in ethanol were then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4 x 10^5 Pa). After 24 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in H_2O and the solution was made basic by the addition of concentrated aqueous NH_4OH solution. The aqueous solution was extracted with 10% MeOH/$CHCl_3$ several times and the combined organic layers were concentrated under reduced pressure. Chromatography (SiO_2, 25-75% CMA/$CHCl_3$) gave an off-white powder. Crystallization from ethyl acetate and methanol gave 125 mg of the desired compound as a white, fluffy solid, mp 207.6 – 208.7 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (d, J = 7.6 Hz, 1H), 7.61 (dd, J = 0.8, 8.3 Hz, 1H), 7.41 (ddd, J = 1.1, 7.1, 8.2 Hz, 1H), 7.23 (ddd, J = 1.2, 7.0, 8.1 Hz, 1H), 6.54 (s, 2H), 5.03 (d, J = 5.9 Hz, 1H), 5.02 (d, J = 15.6 Hz, 1H), 4.94 (d, J = 15.5 Hz, 1H), 4.93 (m, 1H), 4.42 (dd, J = 2.0, 12.0 Hz, 1H), 4.26 (m, 1H), 4.09 (dd, J = 3.6, 12.0 Hz, 1H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.3, 146.8, 145.1, 132.5, 126.9, 126.7, 126.6, 121.4, 121.1, 115.5, 67.0, 64.5, 64.1, 58.7, 20.1; MS (ESI) *m/z* 285 $(M + H)^+$. Anal. calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.16; H, 5.54; N, 19.49.

Example 42

(11*S*)-11-Tetrahydro-2*H*-pyran-4-yl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline



Part A

A solution of methyl tetrahydro-2*H*-pyran-4-carboxylate (13.3 mL, 100 mmol) in 400 mL of anhydrous Et_2O was cooled to -78 °C under N_2. A 1.23 M solution of diisobutylaluminum hydride in hexanes (90 mL, 111 mmol) was then added dropwise to the stirred solution over 40 minutes. The reaction mixture was stirred for an additional 60 minutes, and then treated with 100 mL of saturated aqueous potassium sodium tartrate solution and the mixture was allowed to warm to ambient temperature. The layers were separated and the aqueous portion was extracted with Et_2O (2 x 50 mL). The combined organic portions were washed with 50 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 25-75% ethyl acetate/hexanes) gave 6.64 g of tetrahydro-2*H*-pyran-4-carbaldehyde as a colorless liquid.

Part B

A 500-mL, round-bottomed flask, under an atmosphere of N_2, was charged with sodium hydride (60% oil dispersion, 2.33 g, 58.3 mmol). The sodium hydride was washed with 3 portions of hexanes to remove the oil and then 200 mL of anhydrous THF was

added. Methyltriphenylphosphonium bromide (20.8 g, 58.3 mmol) was then added and the mixture was heated to reflux, under N_2, for 120 minutes. The solution was cooled to ambient temperature and tetrahydro-2*H*-pyran-4-carbaldehyde (5.54 g, 48.6 mmol) was added to the bright yellow reaction mixture via syringe and stirring was continued overnight. Saturated aqueous $NaHCO_3$ solution (100 mL) and 200 mL of Et_2O were added to the reaction mixture and the layers were separated. The organic portion was washed successively with H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a sticky solid. The solid was slurried in a mixture of Et_2O and pentane. The solids were removed by filtration and the filtrate was concentrated under reduced pressure at 0 °C to give a colorless liquid. Chromatography (SiO_2, 20% Et_2O/pentane) gave 1.70 g of 4-vinyltetrahydro-2*H*-pyran as a colorless liquid.

Part C

A 500-mL, round-bottomed flask was charged with potassium ferricyanide (III) (15.0 g, 45.6 mmol), 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinidyl)pyrimidine ($(DHQD)_2$-PYR) (132 mg, 0.15 mmol) and K_2CO_3 (6.29 g, 45.6 mmol). A 1:1 mixture of *tert*-butyl alcohol/H_2O (150 mL) was added and the suspension was stirred under N_2. A 0.25 M solution of OsO_4 in toluene (0.60 mL, 0.15 mmol) was then added the mixture was cooled to 0 °C. After stirring for 60 minutes, 4-vinyltetrahydro-2*H*-pyran (1.70 g, 15.2 mmol) was added and the mixture was stirred overnight. Solid $Na_2S_2O_5$ (22.5 g) was then added and the reaction mixture was allowed to warm to ambient temperature. CH_2Cl_2 (150 mL) was then added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 10% methanol/$CHCl_3$) gave 2.11 g of (1*R*)-1-tetrahydro-2*H*-pyran-4-ylethane-1,2-diol as a colorless oil.

Part D

A solution of (1*R*)-1-tetrahydro-2*H*-pyran-4-ylethane-1,2-diol (2.40 g, 16.2 mmol) in 60 mL of CH_2Cl_2 was cooled to 0 °C under N_2. 2,6-Lutidine (3.77 mL, 32.4 mmol) and *tert*-butyldimethylsilyl chloride (2.57 g, 17.0 mmol) were added and the reaction mixture was stirred and allowed to warm to ambient temperature overnight. The reaction mixture was treated with saturated aqueous NH_4Cl solution and the layers were separated. The organic portion was washed successively with aqueous 3.5% NaH_2PO_4 solution (2x), H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 3.29 g of (1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-tetrahydro-2*H*-pyran-4-ylethanol as a colorless oil.

Part E

A solution of (1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-tetrahydro-2*H*-pyran-4-ylethanol (3.29 g, 12.7 mmol) in 60 mL of CH_2Cl_2 was cooled to 0 °C under N_2. Triethylamine (3.58 mL, 25.7 mmol) was then added followed by methanesulfonyl chloride (2.57 g, 17.0 mmol) and DMAP (61 mg, 0.50 mmol) and the reaction mixture was stirred and allowed to warm to ambient temperature overnight. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution and the layers were separated. The organic portion was washed successively with aqueous 3.5% NaH_2PO_4 solution (2x), H_2O and brine, dried over Na_2SO4, filtered and concentrated under reduced pressure to give 4.29 g of (1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-tetrahydro-2*H*-pyran-4-ylethyl methanesulfonate as a colorless oil.

Part F

A solution of (1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-tetrahydro-2*H*-pyran-4-ylethyl methanesulfonate (4.29 g, 12.7 mmol) in 40 mL of DMF was treated with sodium azide (1.00 g, 15.2 mmol) and the mixture was heated to 60 °C for 12 hours and then to 80 °C for 8 hours. The reaction mixture was concentrated under reduced pressure and the resulting material was dissolved in 50 mL of ethyl acetate and washed successively with H_2O (3 x 25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 10-25% ethyl acetate/hexanes) gave 1.60 g of {[(2*S*)-2-azido-2-tetrahydro-2*H*-pyran-4-ylethyl]oxy}(*tert*-butyl)dimethylsilane as a colorless oil and 1.50 g of recovered (1*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-tetrahydro-2*H*-pyran-4-ylethyl methanesulfonate. The recovered starting material was again subjected to the reaction conditions to afford an additional 0.59 g of product.

Part G

{[(2*S*)-2-Azido-2-tetrahydro-2*H*-pyran-4-ylethyl]oxy}(*tert*-butyl)dimethylsilane (2.19 g, 7.68 mmol) was dissolved in 25 mL of methanol and the solution was placed in a pressure bottle. Palladium on carbon (10%, 250 mg) was then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa). After 18 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and

the combined filtrates were concentrated under reduced pressure to give 1.94 g of (1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-tetrahydro-2*H*-pyran-4-ylethanamine as a colorless syrup.

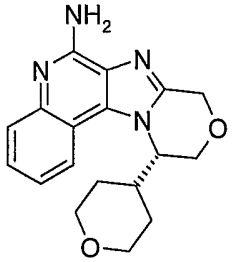
Part H

The title compound was prepared from 4-chloro-3-nitroquinoline and (1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-tetrahydro-2*H*-pyran-4-ylethanamine following Parts E through H listed for the preparation of Example 34. Chromatography (SiO_2, 2-10% methanol/$CHCl_3$) gave a white powder. Crystallization from ethyl acetate gave (11*S*)-11-tetrahydro-2*H*-pyran-4-yl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as colorless crystals, mp 234.0 – 237.0 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (m, 1H), 8.18 (m, 1H), 7.77-7.69 (m, 2H), 7.23 (ddd, J = 1.2, 7.0, 8.1 Hz, 1H), 5.18 (d, J = 16.0 Hz, 1H), 5.07 (d, J = 3.9 Hz, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.49 (d, J = 12.6 Hz, 1H), 4.12 (dd, J = 3.1, 12.6 Hz, 1H), 3.86 (dd, J = 3.2, 11.3 Hz, 1H), 3.76 (dd, J = 3.5, 11.3 Hz, 1H), 3.19 (m, 1H), 2.97 (m, 1H), 2.35 (m, 1H), 1.80-1.55 (m, 3H), 1.10 (d, J = 13.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.6, 144.8, 144.3, 136.5, 132.6, 130.7, 127.2, 127.0, 121.4, 117.9, 67.6, 67.5, 64.5, 64.3, 57.7, 29.4, 28.5; MS (ESI) *m/z* 310 $(M + H)^+$. Anal. calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.87; H, 6.23; N, 13.46.

Example 43

(11*S*)-11-Tetrahydro-2*H*-pyran-4-yl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



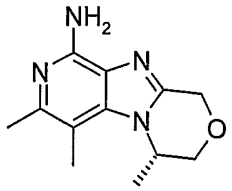
The title compound was prepared from 800 mg of (11*S*)-11-tetrahydro-2*H*-pyran-4-yl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline following Parts I and J listed for the preparation of Example 34. Chromatography (SiO_2, 25-50% CMA/$CHCl_3$) of the title compound gave a light-brown solid. The solid was dissolved in 20 mL of methanol and treated with about 200 mg of activated charcoal. After heating at

reflux for 60 minutes, the reaction mixture was filtered through a CELITE pad. The pad was rinsed with methanol and the combined filtrates were concentrated under reduced pressure. Crystallization from methanol gave 305 mg of the title compound as a fluffy, white solid, mp 240.4 – 243.4 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 0.6, 8.3 Hz, 1H), 7.43 (ddd, J = 0.9, 7.4, 8.0 Hz, 1H), 7.28 (ddd, J = 1.0, 7.1, 8.0 Hz, 1H), 6.58 (s, 2H), 5.10 (d, J = 15.6 Hz, 1H), 4.95 (d, J = 15.8 Hz, 1H), 4.93 (m, 1H), 4.44 (d, J = 12.5 Hz, 1H), 4.08 (dd, J = 2.9, 12.6 Hz, 1H), 3.86 (dd, J = 3.3, 11.1 Hz, 1H), 3.77 (dd, J = 3.3, 11.3 Hz, 1H), 3.19 (m, 1H), 2.98 (m, 1H), 2.30 (m, 1H), 1.80-1.55 (m, 3H), 1.11 (d, J = 13.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.3, 146.2, 145.2, 132.0, 126.9, 126.8, 126.7, 121.5, 120.8, 115.2, 67.7, 67.5, 64.5, 64.3, 57.4, 29.5, 28.5; MS (ESI) m/z 325 (M + H)$^+$. Anal. calcd for $C_{18}H_{20}N_4O_2$•0.25 H2O: C, 65.74; H, 6.28; N, 17.04. Found: C, 65.62; H, 6.25; N, 17.21.

Example 44

(4*S*)-4,6,7-Trimethyl-3,4-dihydro-1*H*-pyrido[3',4':4,5]imidazo[2,1-*c*][1,4]oxazin-9-amine



Part A

A solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (5.0 g, 22.6 mmol) in 50 mL of dry DMF was cooled to 0 °C under an atmosphere of N_2. Triethylamine (6.3 mL, 45.2 mmol) and L-alaninol (2.1 mL, 27.1 mmol) were added sequentially. After approximately 15 minutes, the reaction was allowed to warm to ambient temperature, and then heated to 35 °C for 3 days. The reaction mixture was concentrated under reduced pressure to give an orange-brown solid. The resulting solid was partitioned between 50 mL of ethyl acetate and 50 mL of H_2O. The layers were separated and the organic portion was washed sequentially with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography (SiO_2, 40-60% ethyl acetate/hexanes) afforded (2*S*)-2-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]propan-1-ol (3.62 g) as an orange solid.

Part B

(2*S*)-2-[(2-Chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]propan-1-ol (3.62 g, 13.9 mmol) was dissolved in 30 mL of dry pyridine under an atmosphere of N_2. *tert*-Butyldimethylsilyl chloride (2.52 g, 16.7 mmol) and DMAP (0.17 g, 1.39 mmol) were added sequentially, and the reaction was heated to 50 °C and stirred overnight. The reaction mixture was then concentrated under reduced pressure. The resulting residue was partitioned between 50 mL of ethyl acetate and 50 mL of H_2O. The layers were separated and the organic portion was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting material was passed through a plug of SiO_2, eluting with a mixture of CH_2Cl_2, ethyl acetate and hexanes, to afford *N*-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-5,6-dimethyl-3-nitropyridin-4-amine (4.79 g) as an orange oil.

Part C

A pressure bottle was charged with platinum on carbon (5%, 1.16 g) followed by a solution of *N*-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-5,6-dimethyl-3-nitropyridin-4-amine (4.79 g, 12.8 mmol) dissolved in 125 mL of toluene. The reaction mixture was shaken under H_2 at 48 PSI (3.3×10^5 Pa). After 6 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with toluene and CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to give N^4-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-5,6-dimethylpyridine-3,4-diamine (4.39 g) as an orange oil.

Part D

N^4-((1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-5,6-dimethylpyridine-3,4-diamine (2.85 g, 8.29 mmol) was dissolved in 100 mL of dry 1,2-dichloroethane and the solution was cooled to 0 °C as it stirred under an atmosphere of N_2. Triethylamine (2.3 mL, 16.58 mmol) and chloroacetyl chloride (0.92 mL, 11.60 mmol) were added sequentially. After 30 minutes, the reaction mixture was allowed to warm to ambient temperature and stirred for 3 days followed by heating to 70 °C for 2 days. The reaction mixture was allowed to cool to ambient temperature and was washed with saturated $NaHCO_3$ solution (2 x 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product as a brown solid. Chromatography (SiO_2, 20-50% ethyl acetate/hexanes) gave 1-((1*S*)-2-

{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-4-chloro-2-(chloromethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridine (0.44 g) as a yellow oil.

Part E

1-((1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-4-chloro-2-(chloromethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridine (440 mg, 1.09 mmol) was dissolved in 10 mL of THF and the yellow solution was cooled to –78 °C under an atmosphere of N_2. A 1.0 M solution of tetrabutylammonium fluoride in THF (1.42 mL) was slowly added, and the reaction was allowed to warm to 0 °C overnight. The reaction was then treated with 20 mL of saturated $NaHCO_3$ and 20 mL of CH_2Cl_2. The layers were separated and the organic portion was washed with brine (4 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (2*S*)-2-[4-chloro-2-(chloromethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propan-1-ol (314 mg) as a tan solid. The tan solid was dissolved in 10 mL of anhydrous THF. The resulting yellow solution was cooled to 0 °C under an atmosphere of N_2. Solid potassium *tert*-butoxide (116 mg, 1.42 mmol) was then added and the reaction was stirred at 0 °C for 1 hour and was then allowed to warm to ambient temperature. After 2 hours, the reaction mixture was partitioned between 20 mL of CH_2Cl_2 and 20 mL of saturated $NaHCO_3$ solution. The layers were separated and the organic portion was washed sequentially with 20 mL of saturated $NaHCO_3$ solution and 20 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (4*S*)-9-chloro-4,6,7-trimethyl-3,4-dihydro-1*H*-pyrido[3',4':4,5]imidazo[2,1-*c*][1,4]oxazine (270 mg) as an orange solid.

Part F

A conical microwave vial was charged with a solution of (4*S*)-9-chloro-4,6,7-trimethyl-3,4-dihydro-1*H*-pyrido[3',4':4,5]imidazo[2,1-*c*][1,4]oxazine (270 mg, 1.07 mmol) dissolved in 3.5 mL of 2,2,2-trifluoroethanol. 4-Methoxybenzylamine (1.4 mL, 10.7 mmol) and pyridine hydrochloride (620 mg, 5.35 mmol) were added and the vial was sealed. The solution was heated in an Emrys Optimizer microwave (Personal Chemistry) at 160 °C for 120 minutes. The solvent was removed under reduced pressure, and the resulting residue was partitioned between 20 mL of CH_2Cl_2 and 20 mL of 10% aqueous Na_2CO_3. The layers were separated, and the organic portion was washed with 10% aqueous Na_2CO_3 solution and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressures to give a crude oil. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$)

afforded (4*S*)-*N*-(4-methoxybenzyl)-4,6,7-trimethyl-3,4-dihydro-1*H*-pyrido[3',4':4,5]imidazo[2,1-*c*][1,4]oxazin-9-amine (350 mg) as an orange syrup.

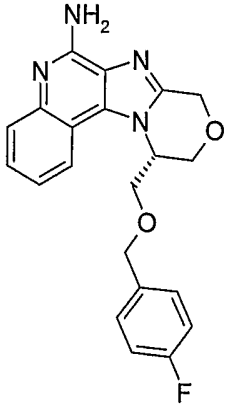
Part G

(4*S*)-*N*-(4-Methoxybenzyl)-4,6,7-trimethyl-3,4-dihydro-1*H*-pyrido[3',4':4,5]imidazo[2,1-*c*][1,4]oxazin-9-amine (350 mg, 0.99 mmol) was dissolved in 15 mL of trifluoroacetic acid and stirred at ambient temperature overnight. The solvent was removed under reduced pressure to give an orange residue which was then treated with 30 mL of aqueous 10% NaOH solution and the mixture was stirred for 2 hours. The solution was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give an orange solid. Chromatography (SiO_2, 10-30% CMA/$CHCl_3$) gave an off-white solid. Crystallization from acetonitrile gave (4*S*)-4,6,7-trimethyl-3,4-dihydro-1*H*-pyrido[3',4':4,5]imidazo[2,1-*c*][1,4]oxazin-9-amine (115 mg) as a white powder, mp 264 – 267 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 5.71 (s, 2H), 4.97 (d, J = 15.6 Hz, 1H), 4.83 (d, J = 15.6 Hz, 1H), 4.80 (s, 1H), 4.02 (s, 2H), 2.38 (s, 3H), 2.31 (s, 3H), 1.43 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.3, 146.2, 145.2, 137.8, 125.0, 103.3, 68.9, 65.0, 49.8, 22.0, 20.6, 12.7; MS (ESI) *m/z* 233 $(M + H)^+$. Anal. calcd for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 61.81; H, 6.93; N, 24.23.

Example 45

(11*S*)-11-{[(4-Fluorobenzyl)oxy]methyl}-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

(11*S*)-11-[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (7.5 g, 22 mmol) was added to a mixture of methanol (270 mL) and acetyl chloride (3.0 mL, 43 mmol) in a pressure bottle. Palladium on carbon (10%, 1.5 g) was then added and the reaction mixture was shaken under H_2 at 48 PSI (3.3 x 10^5 Pa). After 11 days, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with methanol. The combined filtrates were treated with 2 mL of 50% aqueous NaOH solution and the mixture was concentrated under reduced pressure to afford an orange oil. Chromatography (SiO_2, 0-30% CMA/$CHCl_3$) gave an oil that was concentrated from acetonitrile under reduced pressure to give 2.0 g of (11*S*)-11-hydroxymethyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as a tan solid.

Part B

A 100-mL, round-bottomed flask, under an atmosphere of N_2, was charged with sodium hydride (60% oil dispersion, 72 mg, 1.78 mmol). The sodium hydride was washed with 3 portions of hexanes to remove the oil and then 20 mL of anhydrous THF was added. The reaction mixture was cooled to 0 °C and (11*S*)-11-hydroxymethyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (413 mg, 1.62 mmol) was added. After stirring for 75 minutes, 4-fluorobenzyl bromide (215 µL, 1.78 mmol) was added. The reaction was allowed to warm to ambient temperature overnight. After 20 hours the reaction mixture was treated with 20 mL of saturated $NaHCO_3$ solution and 20 mL of ethyl acetate and the layers were separated. The organic portion was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduce pressure to give (11*S*)-11-{[(4-fluorobenzyl)oxy]methyl}-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (580 mg) as a light-yellow, glassy solid.

Part C

(11*S*)-11-{[(4-Fluorobenzyl)oxy]methyl}-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (700 mg, 1.93 mmol) was dissolved in 25 mL of $CHCl_3$ and treated with MCPBA (570 mg, 77% max). The reaction was allowed to stir overnight and then 10 mL of aqueous 2% Na_2CO_3 solution was added and the layers were separated. The aqueous portion was extracted with $CHCl_3$ (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and

concentrated under reduced pressure to afford (11*S*)-11-{[(4-fluorobenzyl)oxy]methyl}-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (732 mg) as an orange foam.

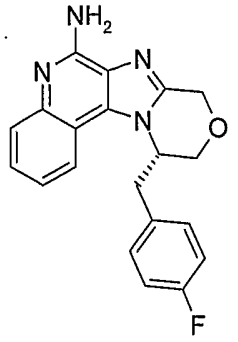
Part D

(11*S*)-11-{[(4-Fluorobenzyl)oxy]methyl}-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (732 mg, 1.93 mmol) was dissolved in 50 mL of CH_2Cl_2 and treated with 5 mL of concentrated NH_4OH solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (370 mg, 1.93 mmol) was carefully added. Rapid stirring continued overnight. The reaction mixture was treated with 5 mL of H_2O, and the layers were separated. The organic portion was washed with saturated $NaHCO_3$ (2 x 50 mL) followed by brine (50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude orange solid. Chromatography (SiO_2, 10-30% CMA/$CHCl_3$) gave 236 mg of (11*S*)-11-{[(4-fluorobenzyl)oxy]methyl}-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a tan solid, mp 134 –137 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.35 (m, 2H), 7.20 (m, 1H), 7.14 (t, *J* = 8.8 Hz, 2H), 6.68 (s, 2H), 5.10 (d, *J* = 15.6 Hz, 1H), 5.07 (m, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 4.87 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 12.2 Hz, 1H), 4.37 (d, *J* = 12.1 Hz, 1H), 4.10 (m, 1H), 3.81–3.78 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.0 (d, *J* = 243.3 Hz), 152.2, 145.7, 145.0, 134.3, 132.0, 130.1 (d, *J* = 8.1 Hz), 127.0, 126.7, 126.5, 121.5, 120.5, 115.4 (d, *J* = 21.3 Hz), 114.7, 72.0, 68.1, 65.0, 64.6, 53.8; MS (APCI) *m/z* 379 $(M + H)^+$. Anal. calcd for $C_{21}H_{19}FN_4O_2 \cdot 0.50\ H_2O$: C, 65.11; H, 5.20; N, 14.46. Found: C, 65.16; H, 5.04; N, 14.42.

Example 46

(11*S*)-11-(4-Fluorobenzyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

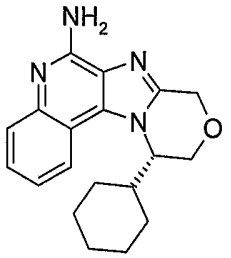


The title compound was prepared from (2*S*)-2-amino-3-(4-fluorophenyl)propan-1-ol, which was prepared from 4-fluoro-L-phenylalanine using the method described by McKennon and Meyers, *J. Org. Chem.*, 58, pp. 3568-3571, (1993), and 3-chloro-4-nitroquinoline following Parts A through G listed for the preparation of Example 1 with the following modifications. Part E was carried out according to the modification described in Part C of Example 11, and Part F was carried out in $CHCl_3$. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white solid. Crystallization from ethanol gave (11*S*)-11-(4-fluorobenzyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white solid, mp 170 – 172 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (d, J = 7.6 Hz, 1H), 7.67 (m, 1H), 7.47 (m, 1H), 7.34 (m, 3H), 7.19 (t, J = 8.8 Hz, 2H), 6.66 (s, 2H), 5.27 (d, J = 10.2 Hz, 1H), 5.08 (d, J = 15.5 Hz, 1H), 4.98 (d, J = 15.5 Hz, 1H), 4.02 (m, 2H), 3.26 (dd, J = 3.7, 14.0 Hz, 1H), 2.51 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6 (d, J = 242.8 Hz), 152.3, 145.5, 145.1, 132.9, 131.7, 131.6 (d, J = 7.9 Hz), 127.0, 126.9, 126.7, 121.6, 120.6, 115.8 (d, J = 21.2 Hz), 114.9, 65.1, 65.0, 55.0, 37.2; MS (ESI) *m/z* 349 $(M + H)^+$. Anal. calcd for $C_{20}H_{17}FN_4O$: C, 68.95; H, 4.92; N, 16.08. Found: C, 68.67; H, 4.86; N, 15.85.

Example 47

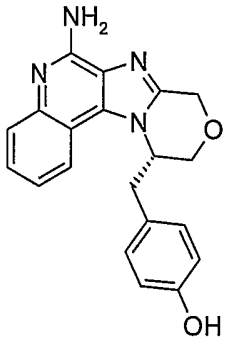
(11*S*)-11-Cyclohexyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



The title compound was prepared from (2*S*)-2-amino-2-cyclohexylethanol, which was prepared from (2*S*)-amino(cyclohexyl)ethanoic acid using the method described by McKennon and Meyers, *J. Org. Chem.*, 58, pp. 3568-3571, (1993), and 3-chloro-4-nitroquinoline following Parts A through G listed for the preparation of Example 1 with the following modifications. Part E was carried out according to the modification described in Part C of Example 11, and Part F was carried out in $CHCl_3$. Crystallization from 1,2-dichloroethane afforded the title compound as a white solid, mp 228 – 230 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 7.4 Hz, 1H), 7.62 (dd, J = 1.1, 8.3 Hz, 1H), 7.43 (m, 1H), 7.27 (m, 1H), 6.58 (s, 2H), 5.08 (d, J = 15.6 Hz, 1H), 4.93 (d, J = 15.6 Hz, 1H), 4.84 (m, 1H), 4.41 (d, J = 12.6 Hz, 1H), 4.06 (dd, J = 3.1, 12.6 Hz, 1H), 2.07 (m, 1H), 1.74 (m, 2H), 1.58 (m, 2H), 1.38 (m, 2H), 1.15 (m, 3H), 0.84 (m, 1H); MS (ESI) 323 *m/z* $(M + H)^+$. Anal. calcd for $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38. Found: C, 70.58; H, 6.66; N, 17.34.

Example 48

4-{[(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methyl}phenol



Part A

4-[(2*S*)-2-Amino-3-hydroxypropyl]phenol (26.8 g, 90.8 mmol), prepared by the method of McKennon and Meyers, *J. Org. Chem.*, 58, pp. 3568-3571, (1993), was suspended in 200 mL of dry CH_2Cl_2 under an atmosphere of N_2. The solution was cooled to 0 °C and sequentially treated with triethylamine (50 mL, 363 mmol) and 3-chloro-4-nitroquinoline (15.79 g, 75.7 mmol). After 30 minutes the reaction mixture was allowed to warm to ambient temperature and stirring was continued overnight. Additional 3-chloro-4-nitroquinoline (2.54 g, 12.2 mmol) was then added, and the reaction mixture was stirred for an additional 4 hours. The reaction mixture was then filtered to give the desired product as a yellow solid. Additional product was obtained by washing the filtrate with saturated $NaHCO_3$ solution (2x) and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure until a yellow solid precipitated from the solution. The yellow solid was isolated by filtration and combined with the first crop to give 21.69 g of 4-{(2*S*)-3-hydroxy-2-[(3-nitroquinolin-4-yl)amino]propyl}phenol.

Part B

4-{(2*S*)-3-Hydroxy-2-[(3-nitroquinolin-4-yl)amino]propyl}phenol (21.69 g, 64.5 mmol) was dissolved in 100 mL of dry pyridine and treated with *tert*-butyldimethylsilyl chloride (22.4 g, 148 mmol) and a catalytic amount of DMAP (0.79 g, 6.45 mmol). The reaction mixture was stirred under N_2 and heated to 40 °C. After 2.5 days, the reaction mixture was concentrated under reduced pressure. The resulting orange residue was partitioned between 200 mL of ethyl acetate and 200 mL of H_2O. The layers were separated and the organic portion was washed sequentially with H_2O and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give *N*-[(1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}benzyl)ethyl]-3-nitroquinolin-4-amine (25.24 g) as an orange solid.

Part C

N-[(1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}benzyl)ethyl]-3-nitroquinolin-4-amine (25.24 g, 44.45 mmol) was dissolved in 300 mL of toluene and the solution was placed in a pressure bottle. Platinum on carbon (5%, 1.47 g) was then added and the reaction mixture was shaken under H_2 at 35 PSI (2.4×10^5 Pa). After 20 hours, the reaction mixture was filtered

through a pad of CELITE filter agent. The pad was rinsed with toluene and acetonitrile and the combined filtrates were concentrated under reduced pressure to give N^4-[(1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}benzyl)ethyl]quinoline-3,4-diamine (23.46 g) as an orange foam.

Part D

N^4-[(1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}benzyl)ethyl]quinoline-3,4-diamine (23.46 g, 43.6 mmol) was dissolved in 400 mL of dry 1,2-dichloroethane and the yellow solution was stirred under N_2. Ethyl 2-chloroethanimidoate hydrochloride (13.8 g, 87.2 mmol) was then added and the reaction mixture was heated to 70 °C overnight. The reaction mixture was then cooled and treated with 300 mL of saturated $NaHCO_3$ solution. The layers were separated and the organic portion was washed sequentially with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography (SiO_2, 10-60% ethyl acetate/hexanes) gave 1-[(1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}benzyl)ethyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (21.11 g) as a brown foam.

Part E

1-[(1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}benzyl)ethyl]-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (21.1 g, 35.4 mmol) was dissolved in 1.5 L of dry CH_2Cl_2 under N_2. The orange solution was cooled to –78 °C and a 1.0 M solution of tetrabutylammonium fluoride in THF (106 mL) was added over 30 minutes. The reaction mixture was allowed to slowly warm to ambient temperature overnight. The reaction mixture was then washed sequentially with saturated $NaHCO_3$ solution and brine (4x). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a red oil. Chromatography (SiO_2, 20-40% CMA/$CHCl_3$) gave 14 g of a viscous brown oil which was then dissolved in CH_2Cl_2 and the solution was washed repeatedly with brine (7x). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a tan foam. Additional purification by column chromatography (SiO_2, 3-6% methanol/CH_2Cl_2) gave 5 g of an off-white solid. The solid was stirred in 150 mL of refluxing 1,2-dichloroethane and then cooled to produce a precipitate. The solid was isolated by filtration to give 2.1 g

of 4-[(11*S*)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-ylmethyl]phenol as a white solid.

Part F

4-[(11*S*)-10,11-Dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-ylmethyl]phenol (2.62 g, 7.91 mmol) was suspended in 50 mL of dry CH_2Cl_2 and stirred under N_2. The solution was treated with triethylamine (2.2 mL, 15.8 mmol) and acetic anhydride (0.89 mL, 9.45 mmol). After 18 hours, the reaction mixture was treated with 50 mL of H_2O. The layers were separated, and the organic portion was washed with H_2O and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 4-[(11*S*)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-ylmethyl]phenyl acetate (2.95 g) as a white solid.

Part G

4-[(11*S*)-10,11-Dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-ylmethyl]phenyl acetate (2.95 g, 7.91 mmol) was dissolved in 80 mL of $CHCl_3$ and treated with MCPBA (2.33 g, 77% max). After stirring for 18 hours, the reaction was treated with 25 mL of a 2% Na_2CO_3 solution and the layers were separated. The aqueous layer was then extracted with $CHCl_3$ (4 x 20 mL). The combined organic layers were washed with 20 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 4-{[(11*S*)-5-oxido-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methyl}phenyl acetate (3.08 g) as a tan solid.

Part H

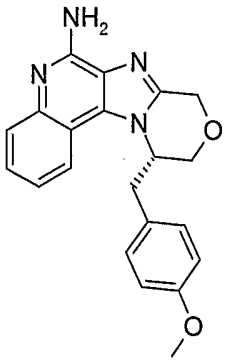
4-{[(11*S*)-5-Oxido-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methyl}phenyl acetate (3.08 g, 7.91 mmol) was dissolved in 100 mL of CH_2Cl_2 and treated with 10 mL of concentrated ammonium hydroxide solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (1.51 g, 7.91 mmol) was carefully added. Rapid stirring continued for 1 hour. The reaction mixture was then treated with 20 mL of H_2O and the layers were separated. The aqueous portion was extracted with CH_2Cl_2 (5 x 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution. Methanol was added to the organic layer to aid in solubility. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a brown solid. Chromatography (SiO_2, 20-40% CMA/$CHCl_3$) gave a yellow solid. This material was dissolved in 100 mL 6 N aqueous HCl, and the solution

was heated at 50 °C overnight. The reaction mixture was cooled and treated with concentrated ammonium hydroxide until pH =11 and then diluted with 200 mL H_2O. The solution was extracted with 9:1 mixture of CH_2Cl_2/methanol (3 x 150 mL). The combined organic layers were washed sequentially with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a white solid. Crystallization from ethanol containing HCl gave 4-{[(11*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methyl}phenol hydrochloride (0.47 g) as an off white solid, mp > 240 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.80 (br s, 2H), 8.27 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.73 (m, 1H), 7.67 (m, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 5.32 (m, 1H), 5.19 (d, J = 15.9 Hz, 1H), 5.06 (d, J = 15.9 Hz, 1H), 4.06 (s, 2H), 3.14 (m, 1H), 3.07 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.4, 149.1, 148.3, 133.8, 133.4, 130.3, 129.5, 125.6, 125.0, 124.5, 121.6, 118.5, 115.4, 112.3, 64.3, 55.6, 48.5, 36.7; MS (ESI) *m/z* 347 $(M + H)^+$. Anal. calcd for $C_{20}H_{18}N_4O_2 \cdot HCl \cdot 0.75$ EtOH: C, 61.87; H, 5.67; N, 13.42; Cl, 8.49. Found: C, 61.46; H, 5.69; N, 13.06; Cl, 8.25.

Example 49

(11*S*)-11-(4-Methoxybenzyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

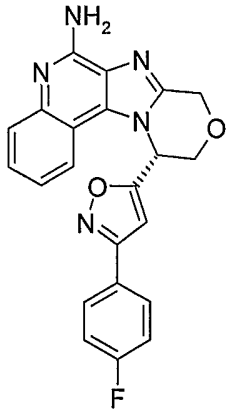


4-{[(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methyl}phenol (80 mg, 0.231 mmol) was dissolved in 3 mL of dry DMF and treated with cesium carbonate (150 mg, 0.462 mmol) under N_2. The reaction mixture was heated to 85 °C for 25 minutes. The reaction mixture was then removed from the heat source and iodomethane (14 μL, 0.231 mmol) was added. The reaction mixture was again heated to 85 °C. After 18 hours, the reaction mixture was cooled and treated with 3 mL of

methanol. The solvents were removed under reduced pressure, and the resulting orange-brown residue was partitioned between 10 mL of CH_2Cl_2 and 10 mL of H_2O. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an orange solid (80 mg). Chromatography (SiO_2, 5-25% CMA/$CHCl_3$) gave the title compound (50 mg) as a yellow solid, mp 115 – 130 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (d, J = 7.6 Hz, 1H), 7.66 (dd, J = 0.8, 8.3 Hz, 1H), 7.47 (m, 1H), 7.36 (m, 1H), 7.26 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 6.60 (s, 2H), 5.21 (m, 1H), 5.10 (d, J = 15.5 Hz, 1H), 4.99 (d, J = 15.5 Hz, 1H), 4.01 (s, 2H), 3.37 (s, 3H), 3.19 (m, 1H), 3.07 (m, 1H); MS (ESI) *m/z* 361 $(M + H)^+$.

Example 50

(11*R*)-11-[3-(4-Fluorophenyl)isoxazol-5-yl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

tert-Butyl (4*S*)-4-ethynyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (2.15 g, 9.55 mmol), prepared by the method of Serrat *et al.*, *Tetrahdron: Asymmetry*, 10, pp. 3417-3430, (1999), was dissolved in 10 mL of ethanol and treated with 10 mL of 3 M HCl in ethanol. The solution was heated to 85 °C for 3 hours and then concentrated to give 1.16 g of (2*S*)-2-aminobut-3-yn-1-ol hydrochloride as a white solid.

Part B

(11*S*)-11-ethynyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline was prepared from (2*S*)-2-aminobut-3-yn-1-ol hydrochloride and 3-chloro-4-nitroquinoline following Parts A through E listed for the preparation of Example 1 with the following modification. Part E was carried out according to the modification

described in Part C of Example 11. Chromatography (5% methanol/$CHCl_3$) gave the desired product as an off-white solid.

Part C

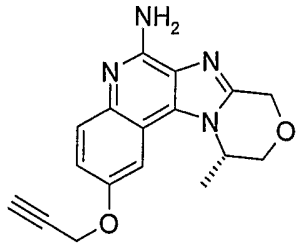
A solution of 4-fluorobenzaldehyde oxime (222 mg, 1.60 mmol) dissolved in 3 mL of DMF was treated with *N*-chlorosuccinimide (212 mg, 1.60 mmol) and the reaction mixture was heated at 50 °C for 3 hours. The reaction mixture was diluted with 25 mL of ethyl acetate and then washed with H_2O (4 x 20 mL). The organic portion was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride as a white solid. The material was dissolved in 10 mL of CH_2Cl_2 and the solution was cooled to 0 °C. A solution of (11*S*)-11-ethynyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (190 mg, 0.76 mmol) dissolved in 3 mL of CH_2Cl_2 was then added followed by triethylamine (318 μL, 2.29 mmol). The reaction was allowed to warm to ambient temperature overnight. The reaction mixture was concentrated and chromatography (0-2% methanol/$CHCl_3$) gave (11*R*)-11-[3-(4-fluorophenyl)isoxazol-5-yl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as a light-brown solid.

Part D

The title compound was prepared from (11*R*)-11-[3-(4-fluorophenyl)isoxazol-5-yl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline following Parts F and G listed for the preparation of Example 1. Chromatography (SiO_2, 10-35% CMA/$CHCl_3$) gave an off-white powder. Crystallization from ethyl acetate with a small amount of methanol gave the title compound as amber crystals, mp 261.0-262.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (m, 2H), 7.71 (d, J = 7.3 Hz, 1H), 7.59 (dd, J = 0.9, 8.4 Hz, 1H), 7.37 (m, 1H), 7.27 (m, 2H), 7.13 (ddd, J = 1.2, 7.0, 8.2 Hz, 1H), 6.87 (s, 1H), 6.68 (s, 2H), 6.65 (m, 1H), 5.23 (d, J = 15.7 Hz, 1H), 5.13 (d, J = 15.8 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.44 (dd, J = 3.1, 12.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 163.2 (d, J = 248 Hz), 161.1, 151.7, 144.83, 144.75, 131.8, 129.0 (d, J = 8.6 Hz), 126.6, 126.4, 126.1, 124.4, 120.9, 120.0, 116.0 (d, J = 21.9 Hz), 114.1, 101.4, 67.2, 64.9, 52.0; MS (ESI) *m/z* 402 $(M + H)^+$. Anal. calcd for $C_{22}H_{16}FN_5O_2 \cdot 0.50\ C_4H_8O_2$: C, 64.71; H, 4.53; N, 15.72. Found: C, 64.49; H, 4.65; N, 15.83.

Example 51

(11*S*)-11-Methyl-2-(prop-2-ynyloxy)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

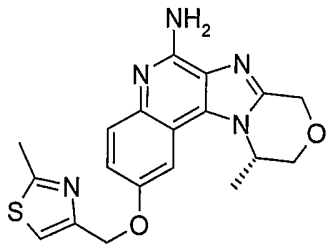


A solution of (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (100 mg, 0.370 mmol) dissolved in 15 mL of DMF was treated with cesium carbonate (241 mg, 0.740 mmol) and propargyl bromide (49 mg, 0.410 mmol) and stirred overnight at ambient temperature. The dark brown mixture was then poured into 150 mL of H_2O and stirred for 30 minutes. The mixture was filtered to give a dark brown solid. Chromatography (SiO_2, 0-30% CMA/$CHCl_3$) followed by crystallization from ethyl acetate gave 51 mg of the title compound as an off-white solid, mp 184-186 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.58 (d, J = 9.0 Hz, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.15 (dd, J = 2.5, 9.0 Hz, 1H), 6.37 (br s, 2H), 5.15 (m, 1H), 5.10 (d, J = 15.6 Hz, 1H), 4.96 (d, J = 15.6 Hz, 1H), 4.93 (d, J = 1.9 Hz, 2H), 4.14 (m, 2H), 3.60 (t, J = 1.9 Hz, 1H), 1.60 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.6, 150.4, 145.0, 139.8, 130.9, 127.3, 126.7, 116.8, 114.2, 103.1, 79.3, 78.1, 68.2, 64.6, 55.7, 49.8, 19.1; MS (APCI) *m/z* 309 $(M + H)^+$. Anal. calcd for $C_{17}H_{16}N_4O_2 \cdot 0.5\ C_4H_8O_2$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.94; H, 5.47; N, 16.10.

Example 52

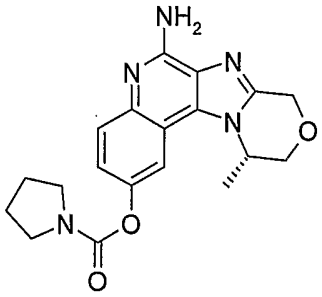
(11*S*)-11-Methyl-2-[(2-methyl-1,3-thiazol-4-yl)methoxy]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



A solution of (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (500 mg, 1.85 mmol) dissolved in 15 mL of DMF was treated with cesium carbonate (1.80 g, 5.55 mmol), 4-chloromethyl-2-methylthiazole hydrochloride (375 mg, 2.03 mmol) and tetrabutylammonium bromide (715 mg, 2.22 mmol). After stirring overnight at 50°C, the dark brown mixture was poured into 150 mL of H_2O and stirred for 30 minutes. The reaction mixture was extracted with $CHCl_3$ (3 x 75 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown solid. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white solid which was crystallized from acetonitrile to give 237 mg of the title compound as an off-white solid, mp 105-107 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.57 (s, 1H), 7.51 (d, J = 2.7 Hz, 1H), 7.19 (dd, J = 2.7, 9.1 Hz, 1H), 6.35 (br s, 2H), 5.25 (m, 2H), 5.14 (m, 1H), 5.09 (d, J = 15.5 Hz, 1H), 4.95 (d, J = 15.5 Hz, 1H), 4.14 (m, 2H), 2.67 (s, 3H), 1.54 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.6, 152.7, 151.5, 150.3, 145.0, 139.6, 130.9, 127.4, 126.7, 117.6, 116.9, 114.3, 102.8, 68.2, 65.6, 64.6, 49.8, 19.0, 18.6; MS (APCI) *m/z* 382 $(M + H)^+$. Anal. calcd for $C_{19}H_{19}N_5O_2 \cdot 0.75\ C_4H_8O_2 \cdot 0.33\ H_2O$: C, 58.88; H, 5.28; N, 19.26. Found: C, 58.62; H, 4.96; N, 19.10.

Example 53

(11*S*)-6-Amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-yl pyrrolidine-1-carboxylate



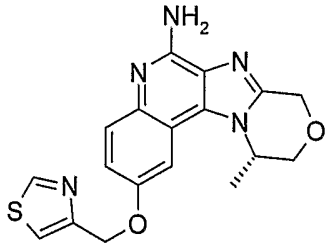
A solution of (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (500 mg, 1.85 mmol) dissolved in 15 mL of DMF was treated with cesium carbonate (1.80 g, 5.55 mmol) and pyrrolidinecarbonyl chloride (275 mg, 2.03 mmol). After stirring overnight at ambient temperature, the light brown mixture was poured into 150 mL of H_2O and stirred for 30

minutes. The reaction mixture was extracted with $CHCl_3$ (3 x 75 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown solid. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white solid which was crystallized from acetonitrile to give 122 mg of the title compound as an off-white solid, mp 218-219 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.71 (d, J = 2.5 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.22 (dd, J = 2.5, 9.0 Hz, 1H), 6.57 (br s, 2H), 5.09 (d, J = 15.5 Hz, 1H), 5.06 (m, 1H), 4.95 (d, J = 15.5 Hz, 1H), 4.11 (m, 2H), 3.56 (m, 2H), 3.37 (m, 2H), 1.96-1.85 (m, 4H), 1.54 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.5, 151.4, 145.2, 145.1, 142.0, 130.9, 126.6, 126.6, 121.4, 113.9, 112.1, 68.2, 64.5, 49.8, 46.1, 45.9, 25.2, 24.3, 18.8; MS (APCI) m/z 368 $(M + H)^+$. Anal. calcd for $C_{19}H_{21}N_5O_3$: C, 62.11; H, 5.76; N, 19.06. Found: C, 61.82; H, 5.63; N, 18.97.

Example 54

(11*S*)-11-Methyl-2-(1,3-thiazol-4-ylmethoxy)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

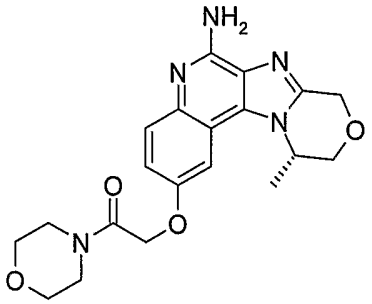


A solution of (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (500 mg, 1.85 mmol) dissolved in 15 mL of DMF was treated with cesium carbonate (1.80 g, 5.55 mmol), 4-chloromethyl thiazole hydrochloride (345 mg, 2.03 mmol), and tetrabutylammonium bromide (715 mg, 2.22 mmol). After stirring overnight at ambient temperature, the brown mixture was poured into 150 mL of H_2O and stirred for 30 minutes. The reaction mixture was extracted with $CHCl_3$ (3 x 75 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown solid. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white solid which was crystallized from acetonitrile to give 179 mg of the title compound as an off-white solid, mp 240-242 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (d, J = 2.0 Hz, 1H), 7.82 (d, J = 1.9 Hz, 1H), 7.58 (d, J = 9.1 Hz, 1H),

7.51 (d, J = 2.7 Hz, 1H), 7.21 (dd, J = 2.6, 9.1 Hz, 1H), 6.35 (br s, 2H), 5.36 (m, 2H), 5.14 (m, 1H), 5.09 (d, J = 15.5 Hz, 1H), 4.95 (d, J = 15.5 Hz, 1H), 4.13 (m, 2H), 1.52 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.4, 152.8, 152.7, 150.3, 145.0, 139.6, 130.9, 127.3, 126.7, 118.0, 116.9, 114.3, 102.8, 68.2, 65.6, 64.5, 49.8, 18.9; MS (APCI) *m/z* 368 (M + H)$^+$. Anal. calcd for $C_{18}H_{17}N_5O_2S$: C, 58.84; H, 4.66; N, 19.06. Found: C, 58.88; H, 4.63; N, 19.29.

Example 55

(11*S*)-11-Methyl-2-(2-morpholin-4-yl-2-oxoethoxy)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

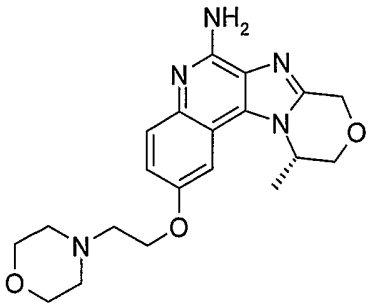


A solution of (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (500 mg, 1.85 mmol) dissolved in 15 mL of DMF was treated with cesium carbonate (1.80 g, 5.55 mmol) and 2-bromo-1-morpholin-4-yl-ethanone (462 mg, 2.03 mmol). After stirring overnight at 75 °C, the brown mixture was poured into 150 mL of H_2O and stirred for 30 minutes. The reaction mixture was extracted with $CHCl_3$ (3 x 75 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an off-white solid. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white solid which was crystallized from acetonitrile to give 272 mg of the title compound as an off-white solid, mp 226-228 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 2.6 Hz, 1H), 7.14 (dd, J = 2.7, 9.1 Hz, 1H), 6.37 (br s, 2H), 5.09 (m, 2H), 4.95 (m, 3H), 4.14 (s, 2H), 3.46-3.63 (m, 8H), 1.55 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.2, 152.4, 150.3, 145.0, 139.6, 130.8, 127.2, 126.7, 116.6, 114.2, 102.7, 68.2, 66.6, 66.0, 64.6, 49.8, 44.8, 41.5, 19.0; MS (APCI) *m/z* 398 (M + H)$^+$. Anal. calcd for $C_{20}H_{23}N_5O_4$: C, 60.44; H, 5.83; N, 17.62. Found: C, 60.58; H, 5.64; N, 17.67.

Example 56

(11*S*)-11-Methyl-2-(2-morpholin-4-ylethoxy)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

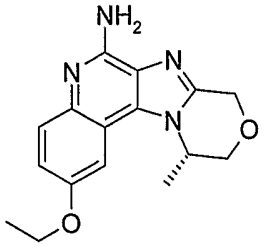


A solution of (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (500 mg, 1.85 mmol) dissolved in 15 mL of DMF was treated with cesium carbonate (1.80 g, 5.55 mmol), 4-(2-chloroethyl) morpholine hydrochloride (378 mg, 2.03 mmol), and tetrabutylammonium bromide (715 mg, 2.22 mmol). After stirring overnight at ambient temperature, the light brown mixture was poured into 150 mL of H_2O and stirred for 30 minutes. The reaction mixture was extracted with $CHCl_3$ (3 x 75 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an off-white solid. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white solid which was crystallized from acetonitrile to give 262 mg of the title compound as an off-white solid, mp 186-188°C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 2.7, 9.1 Hz, 1H), 6.33 (br s, 2H), 5.16 (m, 1H), 5.09 (d, J = 15.5 Hz, 1H), 4.96 (d, J = 15.5 Hz, 1H), 4.26 (m, 1H), 4.17 (m, 1H), 4.12 (m, 2H), 3.61-3.59 (m, 4H), 2.75 (t, J = 5.7 Hz, 2H), 2.52-5.49 (m, 4H), 1.57 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.9, 150.2, 145.0, 139.4, 130.8, 127.4, 126.7, 116.7, 114.3, 102.2, 68.2, 66.0, 65.5, 64.6, 57.0, 53.5, 49.7, 18.9; MS (ESI) *m/z* 384 $(M + H)^+$; Anal. calcd for $C_{20}H_{25}N_5O_3$: C, 62.65; H, 6.57; N, 18.26. Found: C, 62.82; H, 6.39; N, 18.49.

Example 57

(11*S*)-2-Ethoxy-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

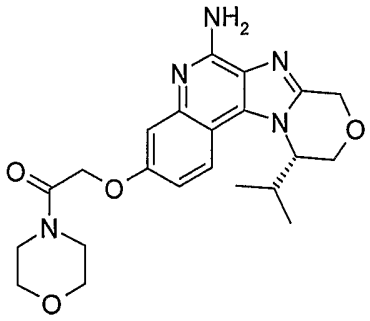


A solution of (11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-2-ol (500 mg, 1.85 mmol) dissolved in 15 mL of DMF was treated with cesium carbonate (1.80 g, 5.55 mmol) and ethyl iodide (346 mg, 2.03 mmol). After stirring overnight at 75 °C, the light brown mixture was poured into 150 mL of H_2O and stirred for 30 minutes. The reaction mixture was extracted with $CHCl_3$ (3 x 75 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown solid. Chromatography (SiO_2, 0-20% CMA/$CHCl_3$) gave an off-white solid which was crystallized from acetonitrile to give 101 mg of the title compound as an off-white solid, mp 187-188°C.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 2.7, 9.0 Hz, 1H), 6.30 (br s, 2H), 5.14 (m, 1H), 5.09 (d, J = 15.5 Hz, 1H), 4.95 (d, J = 15.5 Hz, 1H), 4.21-4.07 (m, 4H), 1.57 (d, J = 6.5 Hz, 3H), 1.39 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.0, 150.2, 144.9, 139.3, 130.8, 127.3, 126.7, 116.5, 114.4, 102.1, 68.2, 64.6, 63.1, 49.8, 18.9, 14.6; MS (ESI) *m/z* 299 $(M + H)^+$. Anal. calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.18; H, 5.89; N, 18.60.

Example 58

(11*S*)-11-Isopropyl-3-(2-morpholin-4-yl-2-oxoethoxy)-10,11-dihydro-8*H*-[1,4] oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

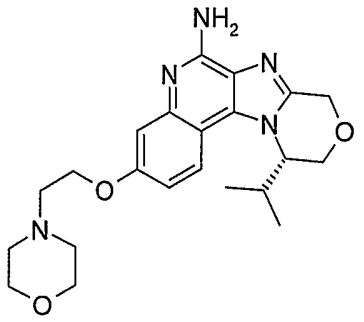


A solution of (11*S*)-6-amino-11- isopropyl -10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-ol (0.30 g, 1.0 mmol) dissolved in 5 mL of DMF was treated with cesium carbonate (1.0 g, 3.0 mmol) and 4-(bromoacetyl)morpholine (0.23 g, 1.1 mmol). After stirring for 18 hours at 65 °C, the reaction mixture was concentrated under reduced pressure to give a solid. The solid was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The organic layer was concentrated under reduced pressure to give a solid. Chromatography (SiO_2, 0-15% CMA/$CHCl_3$) gave a white solid which was crystallized from acetonitrile to give 0.18 g of the title compound as white crystals, mp 137-139 °C.

MS (APCI) *m/z* 426 $(M + H)^+$. Anal. calcd for $C_{22}H_{27}N_5O_4 \cdot 1.5\ H_2O$: C, 58.39; H, 6.68; N, 15.48; Found: C, 58.77; H, 7.36; N, 15.76.

Example 59

(11*S*)-11-Isopropyl-3-(2-morpholin-4-ylethoxy)-10,11-dihydro-8*H*-[1,4] oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

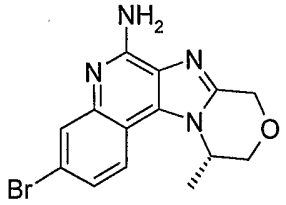


A solution of (11*S*)-6-amino-11- isopropyl -10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-ol (0.30 g, 1.0 mmol) dissolved in 5 mL of DMF was treated with cesium carbonate (1.0 g, 3.0 mmol) and tetrabutylammonium bromide (0.30 g, 1.0 mmol) and a solution of 4-(2-chloroethyl)morpholine hydrochloride (0.21 g, 1.1 mmol). After stirring for 18 hours at 65 °C, the reaction mixture was concentrated under reduced pressure to give a solid. The solid was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The organic layer was concentrated under reduced pressure to give a solid. Chromatography (SiO_2, 0-15% CMA/$CHCl_3$) gave a white solid which was crystallized from acetonitrile to give 110 mg of the title compound as white, mp 194-195 °C.

MS (APCI) *m/z* 412 $(M + H)^+$. Anal. calcd for $C_{22}H_{29}N_5O_3 \cdot 0.25\ H_2O$: C, 63.52; H, 7.15; N, 16.83; Found: C, 63.53; H, 6.96; N, 16.69.

Example 60

(11*S*)-3-Bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A 2-L, three-necked, Morton flask, equipped with overhead stirrer, was charged with 7-bromo-4-chloro-3-nitroquinoline (28.75 g, 100 mmol), anhydrous DMF (200 mL) and triethylamine (28 mL, 200 mmol). The reaction mixture was stirred at ambient temperature and a solution of L-alaninol (7.51 g, 0.1 mol) in 100 mL of DMF was slowly added. After stirring overnight, the reaction mixture was treated with saturated aqueous K_2CO_3 solution (100 ml) and H_2O (800 mL). The mixture was stirred vigorously for 2 hours to produce a yellow precipitate. The yellow solid was collected by vacuum filtration and dried with suction to give 30.9 g of (2*S*)-2-[7-bromo-3-nitroquinolin-4-yl)amino]propan-1-ol as bright-yellow crystals.

Part B

A soluition of (2*S*)-2-[(7-bromo-3-nitroquinolin-4-yl)amino]propan-1-ol (30.0 g, 92.0 mmol) dissolved in 100 mL of anhydrous pyridine was treated with *tert*-butyldimethylsilyl chloride (15.2 g, 101.2 mmol) and a catalytic amount of DMAP (112 mg, 0.92 mmol). After stirring overnight at ambient temperature under an atmosphere of N_2, the reaction mixture was concentrated under reduced pressure. The resulting solid was partitioned between CH_2Cl_2 (500 mL) and H_2O (500 mL). The layers were separated and the organic portion was concentrated under reduced pressure to give 40.5 g of 7-bromo-*N*-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl) -3-nitroquinolin-4-amine as a yellow, crystalline solid.

Part C

A 2-L, stainless-steel, Parr vessel was charged with platinum on carbon (5%, 4.0 g) and 10 mL of acetonitrile. A solution of 7-bromo-*N*-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-3-nitroquinolin-4-amine (40.5 g, 92.0 mmol) dissolved in 1 L of acetonitrile was then added. The reaction mixture was placed on Parr apparatus and shaken under H_2 at 45 PSI (3.1×10^5 Pa) for 6 hours at ambient temperature. The reaction mixture was then filtered through a pad of CELITE filter agent. The pad rinsed with an additional 200 mL of acetonitrile and the combined filtrates were concentrated under reduced pressure to give 33.4 g 7-bromo-N^4-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)quinoline-3,4-diamine as a yellow solid.

Part D

A 1-L, three-necked, Morton flask, equipped with overhead stirrer, was charged with 7-bromo-N^4-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)quinoline-3,4-diamine (33.4 g, 81.0 mmol) and 1,2-dichloroethane (400 mL) and the mixture was stirred under N_2. Ethyl 2-chloroethanimidoate hydrochloride (29.1 g, 184.0 mmol) was then added in portions and the reaction mixture was heated to 70 °C for 3 days. The reaction mixture was then cooled to ambient temperature and treated with $CHCl_3$ (500 mL) and saturated aqueous $NaHCO_3$ solution (700 mL). The layers were separated and the organic portion was concentrated under reduced pressure to give 38 g of 7-bromo-1-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline as a golden solid.

Part E

A 2-L, three-necked, Morton flask, equipped with mechanical stirrer, was charged with 7-bromo-1-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinoline (38.0 g, 81.0 mmol) and 1,2-dichloroethane (900 mL) and the mixture was cooled to 1 °C. A 1.0 M solution of tetrabutylammonium fluoride in THF (90 mL, 90 mmol) was slowly added over 1.5 hours. The reaction temperature was maintained at 1-2 °C during addition. The reaction was allowed to slowly warm to ambient temperature and stirring was continued for 2 days. The reaction was treated with saturated aqueous K_2CO_3 solution (500 mL) and H_2O (400 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined and concentrated under reduced pressure to give a tan solid. Chromatography (SiO_2, 0-6% methanol/CH_2Cl_2) gave 12.5 g of (11*S*)-3-bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as an off-white solid which was used without further purification. A small sample was crystallized from acetonitrile to give white crystals, mp 207-209 °C.

MS (APCI) *m/z* 318 $(M + H)^+$. Anal. calcd for $C_{14}H_{12}BrN_3O \cdot 1.0\ H_2O$: C, 50.02; H, 4.20; N, 12.50. Found: C, 50.19; H, 3.86; N, 12.16.

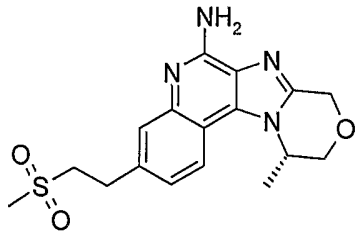
Part F

A 2-L, three-necked, Morton flask, equipped with mechanical stirrer, was charged with (11*S*)-3-bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (9.12 g, 28.7 mmol) and CH_2Cl_2 (500 mL). The mixture was stirred at ambient temperature and MCPBA (10.35 g, 50% purity) was then added slowly in portions. The reaction was stirred at ambient temperature for 2 hours. Concentrated aqueous NH_4OH solution (200 mL) was then slowly added to the reaction mixture followed by careful addition of *p*-toluenesulfonyl chloride (6.29 g, 33.0 mmol) in small portions. The reaction was stirred rapidly at ambient temperature overnight. The reaction was then treated with H_2O (500 mL) and vigorous stirring was maintained for 2 hours. The layers were allowed to separate and a tan precipitate formed. The aqueous layer was removed and the organic layer, containing the precipitate, was filtered to give 6.0 g of (11*S*)-3-bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a tan solid. The product was used in subsequent reactions without further purification.

MS (APCI) *m/z* 333 $(M + H)^+$.

Example 61

(11*S*)-11-Methyl-3-[2-(methylsulfonyl)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino [4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A scintillation vial was charged with palladium acetate (35.2 mg, 0.165 mmol), tri-*o*-tolylphosphine (96 mg, 0.32 mmol), anhydrous DMF (1.0 mL) and triethylamine (1.31 mL, 9.4 mmol). The orange homogeneous solution was then added to a solution of (11*S*)-3-bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (1.00 g, 3.14 mmol) dissolved in 20 mL of anhydrous DMF followed by the addition of a solution of methyl vinyl sulfone (400 mg, 3.77 mmol) dissolved in 1.0 mL of anhydrous DMF. The mixture was transferred to a glass vessel and the vessel was purged with N_2, sealed and heated to 120 °C for 18 hours. The reaction mixture was cooled and concentrated to dryness under reduced pressure to give a golden solid. The solid was treated with CH_2Cl_2 and saturated aqueous K_2CO_3 solution and the layers were separated. The organic layer was concentrated to dryness to give a solid. Chromatography (SiO_2, 0-15% CMA/$CHCl_3$) gave a white solid that was crystallized from acetonitrile to give 0.5 g of (11*S*)-11-methyl-3-[(*E*)-2-(methylsulfonyl)ethenyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as white crystals, mp 249-250 °C.
MS (APCI) *m/z* 344 $(M + H)^+$. Anal. calcd for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24; Found: C, 59.54; H, 4.75; N, 12.06.

Part B

A 250-mL, glass Parr bottle was charged with palladium on carbon (10%, 0.04 g) and 2 mL of ethanol. A solution of (11*S*)-11-methyl-3-[(*E*)-2-(methylsulfonyl)ethenyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (0.45 g, 1.31 mmol) dissolved in 125 mL of ethanol was then added. The reaction mixture was placed on Parr apparatus and shaken under H_2 at 50 PSI (3.4×10^5 Pa) overnight at ambient temperature.

The reaction mixture was then filtered through a pad of CELITE filter agent. The pad rinsed with ethanol and the combined filtrates were concentrated under reduced pressure to give 0.45 g of (11*S*)-11-methyl-3-[2-(methylsulfonyl)ethyl]-10,11-dihydro-8*H*-[1,4] oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as a white solid.

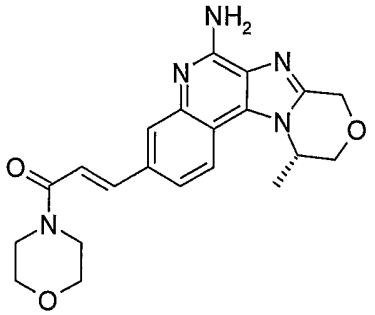
Part C

A 200-mL, round-bottomed flask was charged with (11*S*)-11-methyl-3-[2-(methylsulfonyl)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (0.45 g, 1.31 mmol) and CH_2Cl_2 (75 mL). The mixture was stirred at ambient temperature and MCPBA (0.45 g, 50% purity) was then added slowly in portions. The reaction was stirred at ambient temperature for 2 hours. Concentrated aqueous NH_4OH solution (25 mL) was then slowly added to the reaction mixture followed by careful addition of *p*-toluenesulfonyl chloride (0.27 g, 1.44 mmol). The reaction was stirred rapidly at ambient temperature overnight. The reaction was then treated with H_2O (100 mL) and vigorous stirring was maintained for 2 hours. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were concentrated under reduced pressure. Chromatography (SiO_2, 0-15% CMA/$CHCl_3$) gave a white solid that was crystallized from acetonitrile to give 0.12 g of (11*S*)-11-methyl-3-[2-(methylsulfonyl)ethyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-c]quinolin-6-amine as a white, crystalline solid, mp 205-206 °C.

MS (APCI) *m/z* 361 $(M + H)^+$. Anal. calcd for $C_{17}H_{20}N_4O_3S \cdot 0.66\ H_20$: C, 54.84; H, 5.77; N, 15.05; Found: C, 54.78; H, 5.68; N, 15.04.

Example 62

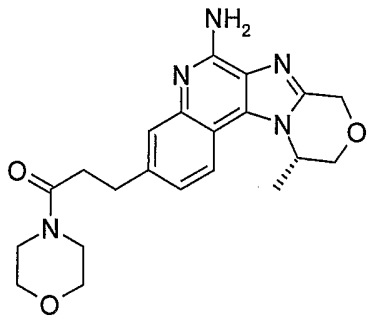
(11*S*)-11-Methyl-3-[(1*E*)-3-morpholin-4-yl-3-oxoprop-1-enyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



A scintillation vial was charged with palladium acetate (22 mg, 0.10 mmol), tri-*o*-tolylphosphine (61 mg, 0.20 mmol), anhydrous DMF (1.0 mL) and triethylamine (0.4 mL, 3.0 mmol). The orange homogeneous solution was then added to a solution of (11*S*)-3-bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (333 mg, 1.00 mmol) dissolved in 10 mL of anhydrous DMF followed by the addition of a solution of 4-acryloylmorpholine (169 mg, 1.20 mmol) dissolved in 1.0 mL of anhydrous DMF. The mixture was transferred to a glass vessel and the vessel was purged with N_2, sealed and heated to 120 °C for 18 hours. The reaction mixture was cooled and concentrated to dryness under reduced pressure to give a golden solid. The solid was treated with CH_2Cl_2 and saturated aqueous K_2CO_3 solution and the layers were separated. The organic layer was concentrated to dryness to give a light-brown solid. Chromatography (SiO_2, 0-15% CMA/$CHCl_3$) gave a tan solid that was crystallized from acetonitrile to give 250 mg of the title compound as beige crystals, mp >250 °C. MS (APCI) *m/z* 394 $(M + H)^+$.Anal. calcd for $C_{21}H_{23}N_5O_3 \cdot 0.3\ CH_3OH$: C, 63.47; H, 6.05; N, 17.38; Found: C, 63.62; H, 5.89; N, 17.15.

Example 63

(11*S*)-11-Methyl-3-(3-morpholin-4-yl-3-oxopropyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



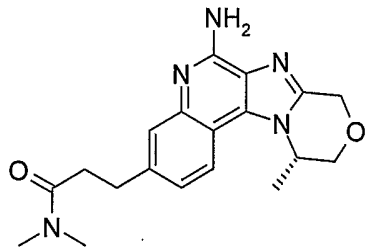
A 250-mL, glass Parr bottle was charged with palladium on carbon (10%, 0.05 g) and 2 mL of ethanol. A solution of (11*S*)-11-methyl-3-[(1*E*)-3-morpholin-4-yl-3-oxoprop-1-enyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (0.25 g, 0.63 mmol) dissolved in 125 mL of a 1:1 mixture of methanol/ethanol was then added. The reaction mixture was placed on Parr apparatus and shaken under H_2 at 50 PSI (3.4 x 10^5 Pa) overnight at ambient temperature. The reaction mixture was treated with additional palladium on carbon (10%, 0.05 g) and shaken under H_2 at 50 PSI (3.4 x 10^5 Pa) for 3

days. The reaction mixture was then filtered through a pad of CELITE filter agent. The pad rinsed with methanol and the combined filtrates were concentrated under reduced pressure to give a white solid. Chromatography (SiO_2, 0-15% CMA/$CHCl_3$) gave a white solid that was crystallized from acetonitrile to give 111 mg of the title compound as white crystals, mp 245-247 °C.

MS (APCI) *m/z* 396 $(M + H)^+$. Anal. calcd for $C_{21}H_{25}N_5O_3$: C, 63.78; H, 6.37; N, 17.71; Found: C, 63.81; H, 6.31; N, 17.73.

Example 64

3-[(11*S*)-6-Amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2] imidazo[4,5-*c*]quinolin-3-yl]-*N*,*N*-dimethylpropanamide



Part A

A scintillation vial was charged with palladium acetate (22 mg, 0.10 mmol), tri-*o*-tolylphosphine (61 mg, 0.20 mmol), anhydrous DMF (1.0 mL) and triethylamine (0.4 mL, 3.0 mmol). The orange homogeneous solution was then added to a solution of (11*S*)-3-bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (333 mg, 1.00 mmol) dissolved in 10 mL of anhydrous DMF followed by the addition of a solution of *N*,*N*-dimethylacrylamide (120 mg, 1.20 mmol) dissolved in 1.0 mL of anhydrous DMF. The mixture was transferred to a glass vessel and the vessel was purged with N_2, sealed and heated to 120 °C for 18 hours. The reaction mixture was cooled and concentrated to dryness under reduced pressure to give a golden solid. The solid was treated with CH_2Cl_2 and saturated aqueous K_2CO_3 solution and the layers were separated. The organic layer was concentrated to dryness to give a light-brown solid. Chromatography (SiO_2, 0-15% CMA/$CHCl_3$) gave a white solid that was crystallized from acetonitrile to give 210 mg of the (2*E*)-3-[(11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-yl]-*N*,*N*-dimethylprop-2-enamide as off-white crystals, mp >250 °C.

MS (APCI) *m/z* 352 $(M + H)^+$.

Part B

A 250-mL, glass Parr bottle was charged with palladium on carbon (10%, 0.05 g) and 2 mL of ethanol. A solution of (2*E*)-3-[(11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-yl]-*N*,*N*-dimethylprop-2-enamide (210 mg, 0.60 mmol) dissolved in 50 mL of ethanol was then added. The reaction mixture was placed on Parr apparatus and shaken under H_2 at 50 PSI (3.4×10^5 Pa) overnight at ambient temperature. The reaction mixture was treated with additional palladium on carbon (10%, 0.05 g) and shaken under H_2 at 50 PSI (3.4×10^5 Pa) for 24 hours. The reaction mixture was then filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and the combined filtrates were concentrated under reduced pressure to give a white solid. Chromatography (SiO_2, 0-15% CMA/$CHCl_3$) gave a white solid that was crystallized from acetonitrile to give 120 mg of 3-[(11*S*)-6-amino-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-3-yl]-*N*,*N*-dimethylpropanamide as white crystals, mp 235-237 °C.

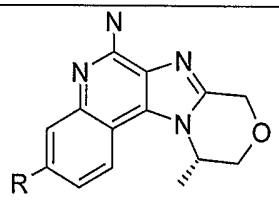
MS (APCI) *m/z* 354 $(M + H)^+$. Anal. calcd for $C_{19}H_{23}N_5O_2 \cdot 0.5\ H_2O$: C, 62.97; H, 6.67; N, 19.32; Found: C, 62.65; H, 6.68; N, 19.01.

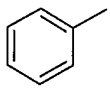
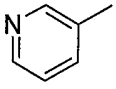
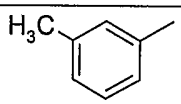
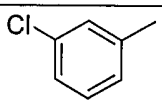
Examples 65 – 73

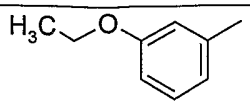
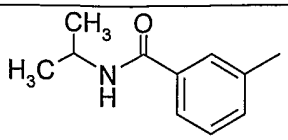
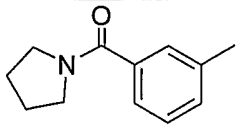
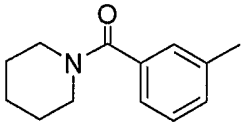
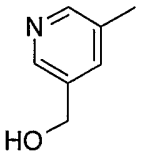
A solution of (11*S*)-3-bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (16 mg, 0.10 mmol) in 7:3 volume:volume (v:v) chloroform:methanol (2 mL) was added to a test tube, and the solvent was removed by vacuum centrifugation. The boronic acid (0.11 mmol) indicated in the table below and *n*-propanol (1.6 mL) were sequentially added. The test tube was purged with nitrogen. Palladium (II) acetate (150 µL of a 4 mg/mL solution in toluene, 0.0026 mmol), 2 M aqueous sodium carbonate solution (600 µL), deionized water (113 µL), and a solution of 0.15 mol% triphenylphosphine in *n*-propanol (53 µL, 0.0078 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath. For Example 73, glacial acetic acid (500 µL), tetrahydrofuran (500 µL), and deionized water (500 µL) were added to the test tube. The reaction was heated for 4 hours at 60 °C.

The contents of each test tube were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the following procedure. Hydrochloric acid (3 mL of 1 N) was added to adjust each example to pH <5, and the resulting solution was passed through the cartridge optionally using light nitrogen pressure. The cartridge was washed with methanol (5 mL) optionally using light nitrogen pressure and transferred to a clean test tube. A solution of 1N ammonia in methanol (2 x 5 mL) was then passed through the cartridge optionally using light nitrogen pressure, and the eluent was collected and concentrated by vacuum centrifugation.

The compounds were purified by preparative high performance liquid chromatography using a Waters FractionLynx automated purification system. The fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. The fractions were collected by mass-selective triggering. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

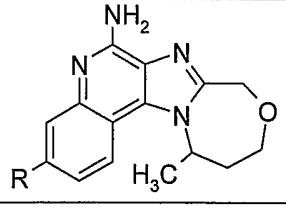


Example	Reagent	R	Measured Mass (M+H)
65	Phenylboronic acid		331.1588
66	Pyridine-3-boronic acid		332.1479
67	3-Methylphenylboronic acid		345.1736
68	3-Chlorophenylboronic acid		365.1198

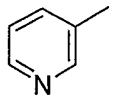
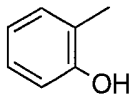
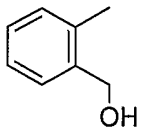
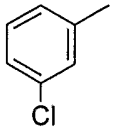
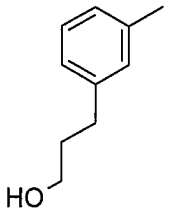
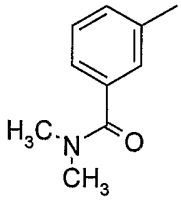
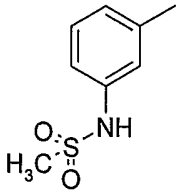
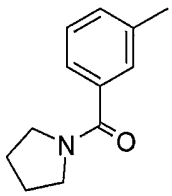
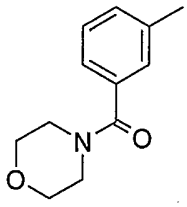
69	3-Ethoxyphenylboronic acid		375.1798
70	3-(*N*-Isopropylaminocarbonyl)phenylboronic acid		416.2074
71	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		428.2053
72	3-(Piperidine-1-carbonyl)phenylboronic acid		442.2257
73	5-(*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid		362.1602

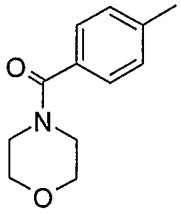
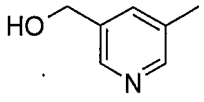
Examples 74 – 85

The compounds in the table below were prepared and purified according to the methods of Examples 65 – 73 except that 3-bromo-12-methyl-11,12-dihydro-8*H*,10*H*-[1,4]oxazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine was used in lieu of (11*S*)-3-bromo-11-methyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine. Example 85 was prepared according to the method used for Example 73. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



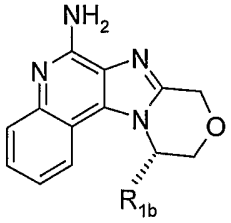
Example	Reagent	R	Measured Mass (M+H)
74	Phenylboronic acid		345.1737

75	Pyridine-3-boronic acid		346.1703
76	(2-Hydroxyphenyl)boronic acid		361.1657
77	(2-Hydroxymethylphenyl)boronic acid dehydrate		375.1823
78	3-Chlorophenylboronic acid		379.1333
79	[3-(Hydroxypropyl)phenyl]boronic acid		403.2138
80	3-(*N*,*N*-Dimethylaminocarbonyl)phenylboronic acid		416.2076
81	3-(Methanesulfonyl)phenylboronic acid		438.1592
82	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		442.2242
83	3-(Morpholine-4-carbonyl)phenylboronic acid		458.2185

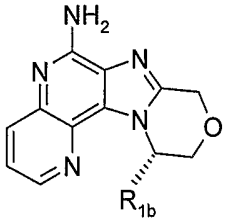
84	4-(Morpholine-4-carbonyl)phenylboronic acid		458.2190
85	5-(*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid		376.1790

Exemplary Compounds

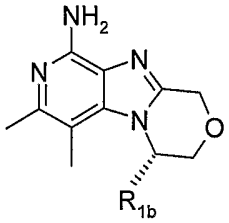
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIa, Va, or VIIa) and the following R_{1b} substituents, wherein each line of the table is matched with Formula IIIa, Va, or VIIa to represent a specific embodiment of the invention.



IIIa



Va

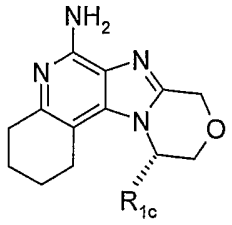


VIIa

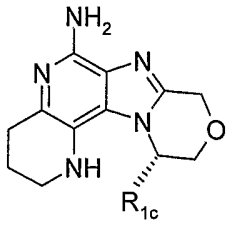
R_{1b}
methyl
isopropyl
1-fluoro-1-methylethyl
1-hydroxy-1-methylethyl
phenyl
benzyl
1-hydroxyethyl
tetrahydro-2*H*-pyran-4-yl

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IVb or VIb) and the following R_{1c} substituents,

wherein each line of the table is matched with Formula IVb or VIb to represent a specific embodiment of the invention.



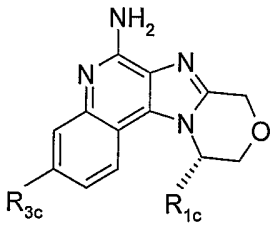
IVb



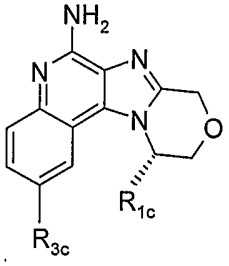
VIb

R_{1c}
methyl
isopropyl
1-fluoro-1-methylethyl
1-hydroxy-1-methylethyl
1-hydroxyethyl
tetrahydro-2*H*-pyran-4-yl

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIb or IIIc) and the following R_{1c} and R_{3c} substituents, wherein each line of the table is matched with Formula IIIb or IIIc to represent a specific embodiment of the invention.



IIIb



IIIc

R_{1c}	R_{3c}
methyl	2-cyanoethyl
methyl	2-(aminocarbonyl)ethyl

R_{1c}	R_{3c}
methyl	3-aminopropyl
methyl	3-(acetylamino)propyl
methyl	3-[(methylsulfonyl)amino]propyl
methyl	3-{[(isopropylamino)carbonyl]amino}propyl
methyl	2-aminoethyl
methyl	2-(acetylamino)ethyl
methyl	2-[(methylsulfonyl)amino]ethyl
methyl	2-{[(isopropylamino)carbonyl]amino}ethyl
methyl	3-ethoxy-3-oxopropyl
methyl	2-carboxyethyl
methyl	ethenyl
methyl	ethyl
methyl	2-oxopyrrolidin-1-yl
methyl	2-oxo-1,3-oxazolidin-3-yl
methyl	(cyclopropylmethyl)amino
methyl	2-(pyridin-3-yl)ethyl
methyl	(1-methyl-1*H*-imidazol-2-yl)methoxy
methyl	(1,3-thiazol-4-yl)methoxy
methyl	(pyridin-3-yl)methoxy
methyl	3-(pyridin-3-yl)propoxy
methyl	(1-acetylpiperidin-4-yl)oxy
methyl	{1-[(isopropylamino)carbonyl]piperidin-4-yl}oxy
methyl	[1-(methylsulfonyl)piperidin-4-yl]oxy
methyl	2-(methylsulfonyl)ethoxy
methyl	2-[(methylsulfonyl)amino]ethoxy
isopropyl	2-cyanoethyl
isopropyl	2-(aminocarbonyl)ethyl
isopropyl	3-aminopropyl
isopropyl	3-(acetylamino)propyl
isopropyl	3-[(methylsulfonyl)amino]propyl

R_{1c}	R_{3c}
isopropyl	3-{[(isopropylamino)carbonyl]amino}propyl
isopropyl	2-aminoethyl
isopropyl	2-(acetylamino)ethyl
isopropyl	2-[(methylsulfonyl)amino]ethyl
isopropyl	2-{[(isopropylamino)carbonyl]amino}ethyl
isopropyl	3-ethoxy-3-oxopropyl
isopropyl	2-carboxyethyl
isopropyl	ethenyl
isopropyl	ethyl
isopropyl	2-oxopyrrolidin-1-yl
isopropyl	2-oxo-1,3-oxazolidin-3-yl
isopropyl	(cyclopropylmethyl)amino
isopropyl	2-(pyridin-3-yl)ethyl
isopropyl	(1-methyl-1*H*-imidazol-2-yl)methoxy
isopropyl	(1,3-thiazol-4-yl)methoxy
isopropyl	(pyridin-3-yl)methoxy
isopropyl	3-(pyridin-3-yl)propoxy
isopropyl	(1-acetylpiperidin-4-yl)oxy
isopropyl	{1-[(isopropylamino)carbonyl]piperidin-4-yl}oxy
isopropyl	[1-(methylsulfonyl)piperidin-4-yl]oxy
isopropyl	2-(methylsulfonyl)ethoxy
isopropyl	2-[(methylsulfonyl)amino]ethoxy
1-fluoro-1-methylethyl	2-cyanoethyl
1-fluoro-1-methylethyl	2-(aminocarbonyl)ethyl
1-fluoro-1-methylethyl	3-aminopropyl
1-fluoro-1-methylethyl	3-(acetylamino)propyl
1-fluoro-1-methylethyl	3-[(methylsulfonyl)amino]propyl
1-fluoro-1-methylethyl	3-{[(isopropylamino)carbonyl]amino}propyl
1-fluoro-1-methylethyl	2-aminoethyl
1-fluoro-1-methylethyl	2-(acetylamino)ethyl

R_{1c}	R_{3c}
1-fluoro-1-methylethyl	2-[(methylsulfonyl)amino]ethyl
1-fluoro-1-methylethyl	2-{[(isopropylamino)carbonyl]amino}ethyl
1-fluoro-1-methylethyl	3-ethoxy-3-oxopropyl
1-fluoro-1-methylethyl	2-carboxyethyl
1-fluoro-1-methylethyl	ethenyl
1-fluoro-1-methylethyl	ethyl
1-fluoro-1-methylethyl	2-oxopyrrolidin-1-yl
1-fluoro-1-methylethyl	2-oxo-1,3-oxazolidin-3-yl
1-fluoro-1-methylethyl	(cyclopropylmethyl)amino
1-fluoro-1-methylethyl	2-(pyridin-3-yl)ethyl
1-fluoro-1-methylethyl	(1-methyl-1*H*-imidazol-2-yl)methoxy
1-fluoro-1-methylethyl	(1,3-thiazol-4-yl)methoxy
1-fluoro-1-methylethyl	(pyridin-3-yl)methoxy
1-fluoro-1-methylethyl	3-(pyridin-3-yl)propoxy
1-fluoro-1-methylethyl	(1-acetylpiperidin-4-yl)oxy
1-fluoro-1-methylethyl	3-(pyridin-3-yl)propoxy
1-fluoro-1-methylethyl	{1-[(isopropylamino)carbonyl]piperidin-4-yl}oxy
1-fluoro-1-methylethyl	[1-(methylsulfonyl)piperidin-4-yl]oxy
1-fluoro-1-methylethyl	2-(methylsulfonyl)ethoxy
1-fluoro-1-methylethyl	2-[(methylsulfonyl)amino]ethoxy
1-hydroxy-1-methylethyl	2-cyanoethyl
1-hydroxy-1-methylethyl	2-(aminocarbonyl)ethyl
1-hydroxy-1-methylethyl	3-aminopropyl
1-hydroxy-1-methylethyl	3-(acetylamino)propyl
1-hydroxy-1-methylethyl	3-[(methylsulfonyl)amino]propyl
1-hydroxy-1-methylethyl	3-{[(isopropylamino)carbonyl]amino}propyl
1-hydroxy-1-methylethyl	2-aminoethyl
1-hydroxy-1-methylethyl	2-(acetylamino)ethyl
1-hydroxy-1-methylethyl	2-[(methylsulfonyl)amino]ethyl
1-hydroxy-1-methylethyl	2-{[(isopropylamino)carbonyl]amino}ethyl

R_{1c}	R_{3c}
1-hydroxy-1-methylethyl	3-ethoxy-3-oxopropyl
1-hydroxy-1-methylethyl	2-carboxyethyl
1-hydroxy-1-methylethyl	ethenyl
1-hydroxy-1-methylethyl	ethyl
1-hydroxy-1-methylethyl	2-oxopyrrolidin-1-yl
1-hydroxy-1-methylethyl	2-oxo-1,3-oxazolidin-3-yl
1-hydroxy-1-methylethyl	(cyclopropylmethyl)amino
1-hydroxy-1-methylethyl	2-(pyridin-3-yl)ethyl
1-hydroxy-1-methylethyl	(1-methyl-1*H*-imidazol-2-yl)methoxy
1-hydroxy-1-methylethyl	(1,3-thiazol-4-yl)methoxy
1-hydroxy-1-methylethyl	(pyridin-3-yl)methoxy
1-hydroxy-1-methylethyl	3-(pyridin-3-yl)propoxy
1-hydroxy-1-methylethyl	(1-acetylpiperidin-4-yl)oxy
1-hydroxy-1-methylethyl	{1-[(isopropylamino)carbonyl]piperidin-4-yl}oxy
1-hydroxy-1-methylethyl	[1-(methylsulfonyl)piperidin-4-yl]oxy
1-hydroxy-1-methylethyl	2-(methylsulfonyl)ethoxy
1-hydroxy-1-methylethyl	2-[(methylsulfonyl)amino]ethoxy
1-hydroxyethyl	2-cyanoethyl
1-hydroxyethyl	2-(aminocarbonyl)ethyl
1-hydroxyethyl	3-aminopropyl
1-hydroxyethyl	3-(acetylamino)propyl
1-hydroxyethyl	3-[(methylsulfonyl)amino]propyl
1-hydroxyethyl	3-{[(isopropylamino)carbonyl]amino}propyl
1-hydroxyethyl	2-aminoethyl
1-hydroxyethyl	2-(acetylamino)ethyl
1-hydroxyethyl	2-[(methylsulfonyl)amino]ethyl
1-hydroxyethyl	2-{[(isopropylamino)carbonyl]amino}ethyl
1-hydroxyethyl	3-ethoxy-3-oxopropyl
1-hydroxyethyl	2-carboxyethyl
1-hydroxyethyl	ethenyl

R_{1c}	R_{3c}
1-hydroxyethyl	ethyl
1-hydroxyethyl	2-oxopyrrolidin-1-yl
1-hydroxyethyl	2-oxo-1,3-oxazolidin-3-yl
1-hydroxyethyl	(cyclopropylmethyl)amino
1-hydroxyethyl	2-(pyridin-3-yl)ethyl
1-hydroxyethyl	(1-methyl-1*H*-imidazol-2-yl)methoxy
1-hydroxyethyl	(1,3-thiazol-4-yl)methoxy
1-hydroxyethyl	(pyridin-3-yl)methoxy
1-hydroxyethyl	3-(pyridin-3-yl)propoxy
1-hydroxyethyl	(1-acetylpiperidin-4-yl)oxy
1-hydroxyethyl	{1-[(isopropylamino)carbonyl]piperidin-4-yl}oxy
1-hydroxyethyl	[1-(methylsulfonyl)piperidin-4-yl]oxy
1-hydroxyethyl	2-(methylsulfonyl)ethoxy
1-hydroxyethyl	2-[(methylsulfonyl)amino]ethoxy
tetrahydro-2*H*-pyran-4-yl	2-cyanoethyl
tetrahydro-2*H*-pyran-4-yl	2-(aminocarbonyl)ethyl
tetrahydro-2*H*-pyran-4-yl	3-aminopropyl
tetrahydro-2*H*-pyran-4-yl	3-(acetylamino)propyl
tetrahydro-2*H*-pyran-4-yl	3-[(methylsulfonyl)amino]propyl
tetrahydro-2*H*-pyran-4-yl	3-{[(isopropylamino)carbonyl]amino}propyl
tetrahydro-2*H*-pyran-4-yl	2-aminoethyl
tetrahydro-2*H*-pyran-4-yl	2-(acetylamino)ethyl
tetrahydro-2*H*-pyran-4-yl	2-[(methylsulfonyl)amino]ethyl
tetrahydro-2*H*-pyran-4-yl	2-{[(isopropylamino)carbonyl]amino}ethyl
tetrahydro-2*H*-pyran-4-yl	3-ethoxy-3-oxopropyl
tetrahydro-2*H*-pyran-4-yl	2-carboxyethyl
tetrahydro-2*H*-pyran-4-yl	ethenyl
tetrahydro-2*H*-pyran-4-yl	ethyl
tetrahydro-2*H*-pyran-4-yl	2-oxopyrrolidin-1-yl
tetrahydro-2*H*-pyran-4-yl	2-oxo-1,3-oxazolidin-3-yl

R_{1c}	R_{3c}
tetrahydro-2*H*-pyran-4-yl	(cyclopropylmethyl)amino
tetrahydro-2*H*-pyran-4-yl	2-(pyridin-3-yl)ethyl
tetrahydro-2*H*-pyran-4-yl	(1-methyl-1*H*-imidazol-2-yl)methoxy
tetrahydro-2*H*-pyran-4-yl	(1,3-thiazol-4-yl)methoxy
tetrahydro-2*H*-pyran-4-yl	(pyridin-3-yl)methoxy
tetrahydro-2*H*-pyran-4-yl	3-(pyridin-3-yl)propoxy
tetrahydro-2*H*-pyran-4-yl	(1-acetylpiperidin-4-yl)oxy
tetrahydro-2*H*-pyran-4-yl	{1-[(isopropylamino)carbonyl]piperidin-4-yl}oxy
tetrahydro-2*H*-pyran-4-yl	[1-(methylsulfonyl)piperidin-4-yl]oxy
tetrahydro-2*H*-pyran-4-yl	2-(methylsulfonyl)ethoxy
tetrahydro-2*H*-pyran-4-yl	2-[(methylsulfonyl)amino]ethoxy

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention, particularly compounds of the Formulas II, IIa, III, IV, V, VI, and VII wherein Z is -O-, have been found to induce cytokine biosynthesis when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI

complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS

(High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using

HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) on each plate. The solution of test compound is added at 7.5 mM to the first well of a dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μM) than the final tested concentration range.

Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014 μM) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is 2x10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4°C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70°C until analysis.

Interferon-α and Tumor Necrosis Factor-α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF-α and human IFN-α that have been pre-coated on specific spots. Each well contains four spots: one human TNF-α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine serum albumin spots. The human TNF-α capture and detection antibody pair is from MesoScale Discovery. The human IFN-α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN-α subtypes except IFN-α F (IFNA21). Standards consist of recombinant human TNF-α (R&D Systems, Minneapolis, MN) and IFN-α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN-α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the IFN-α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α or IFN-α (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN-α, TNF-α) are reported. Data from plates with scaling factors outside the above

mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

Certain compounds of the invention, particularly compounds of Formulas II-1, II-1a, III-1, IV-1, V-1, VI-1, and VII-1, or compounds of Formulas II, IIa, III, IV, V, VI, and VII wherein Z is -N(-Y-R_2)-, may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below.

TNF-α INHIBITION IN MOUSE CELLS

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor-α (TNF-α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3 x 10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 µL) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3 x 10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5µM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by a dose response assay.

Incubation

A solution of test compound (1µl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 µL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 µL) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1 x 10^5 cells/well. The plates are incubated for 3 hours.

Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

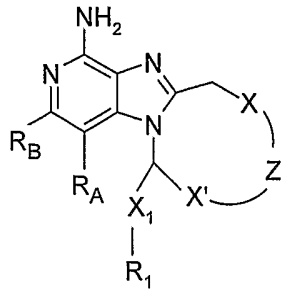
TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

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 compound of the Formula I:



I

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso

that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

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 when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and 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' is a non-interfering substituent;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

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

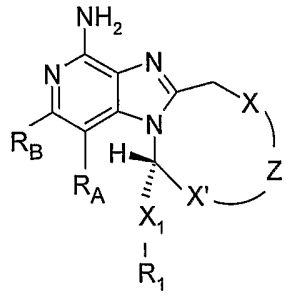
or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

3. A compound of the Formula II:



II

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

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 when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and 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' is a non-interfering substituent;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

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

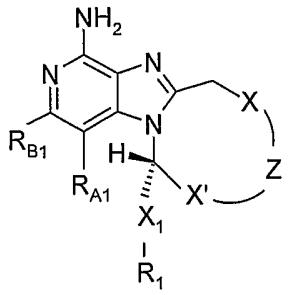
or a pharmaceutically acceptable salt thereof.

4. The compound or salt of claim 3 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

5. A compound of the Formula IIa:



IIa

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of

arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

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 when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and 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_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

R_3 is selected from the group consisting of:

$-Y''-R_4$,

$-Z'-R_4$,

$-Z'-X''-R_4$,

$-Z'-X''-Y'-R_4$,

$-Z'-X''-Y'-X''-Y'-R_4$, 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;

Y' is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

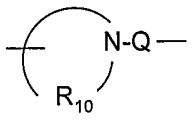
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

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

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

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



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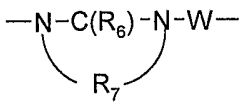

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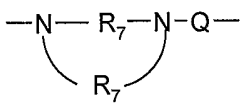

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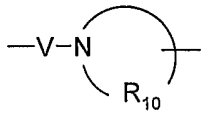

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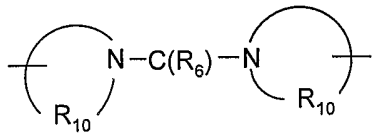

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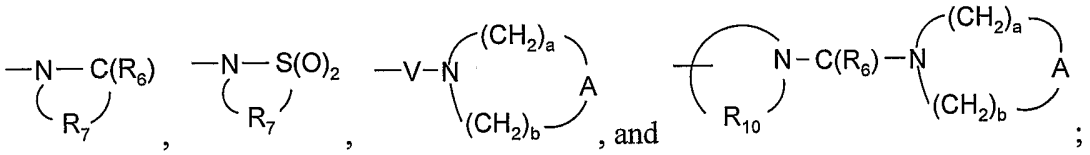
Y" is $-O-C(R_6)-$;

Z' is a bond or -O-;

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_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, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

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 $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

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

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.

6. The compound or salt of claim 5 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and

R_3 is selected from the group consisting of:

-Z'-R_4,

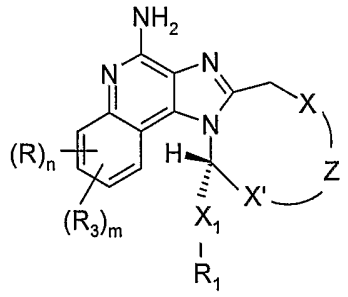
-Z'-X''-R_4,

-Z'-X''-Y'-R_4,

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

-Z'-X''-R_5.

7. A compound of the Formula III:



III

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

R_3 is selected from the group consisting of:

$-Y''-R_4$,

$-Z'-R_4$,

$-Z'-X''-R_4$,

$-Z'-X''-Y'-R_4$,

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

$-Z'-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

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;

Y' is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

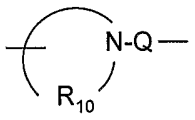
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

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

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

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



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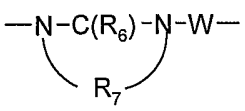

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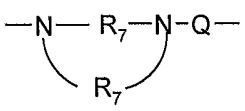

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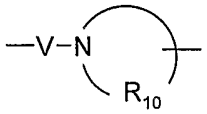
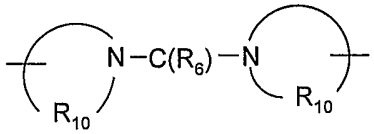


, and



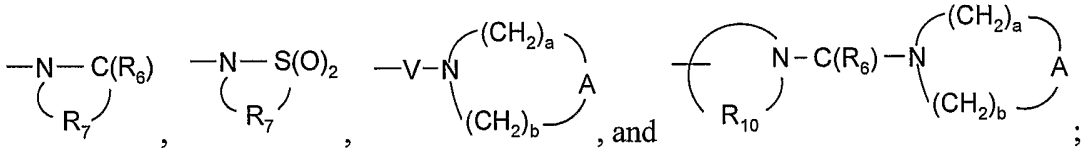
;

Y'' is $-O-C(R_6)-$;

Z' is a bond or -O-;

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_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, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

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 $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

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

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.

8. The compound or salt of claim 7 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and

R_3 is selected from the group consisting of:

-Z'-R_4,

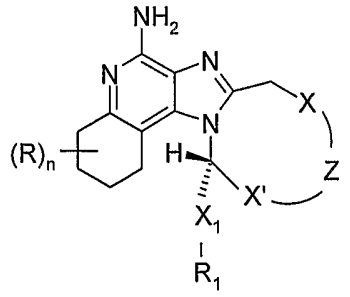
-Z'-X"-R_4,

-Z'-X"-Y'-R_4,

-Z'-X"-Y'-X"-Y'-R_4, and

-Z'-X"-R_5.

9. A compound of the Formula IV:



IV

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of

arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

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

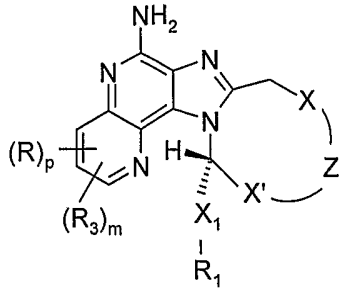
or a pharmaceutically acceptable salt thereof.

10. The compound or salt of claim 9 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

11. A compound of the Formula V:



V

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of

arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

p is an integer from 0 to 3;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

R_3 is selected from the group consisting of:

$-Y''-R_4$,

$-Z'-R_4$,

$-Z'-X''-R_4$,

$-Z'-X''-Y'-R_4$,

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

$-Z'-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

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;

Y' is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

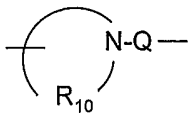
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

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

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

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



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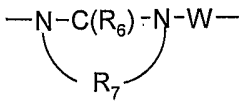
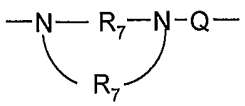

,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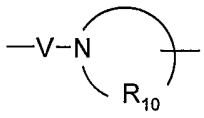
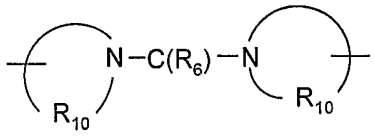

, and

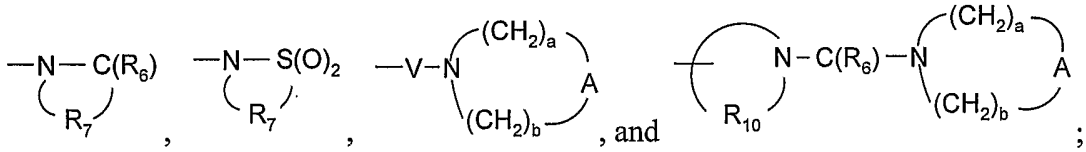

;

Y" is -O-C(R_6)-;

Z' is a bond or -O-;

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_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, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

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 $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

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

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.

12. The compound or salt of claim 11 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and

R_3 is selected from the group consisting of:

$-Z'-R_4$,

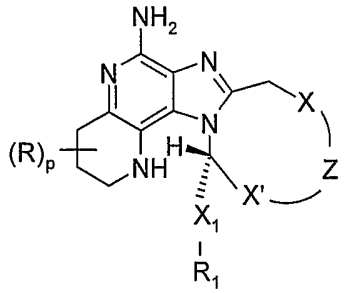
$-Z'-X''-R_4$,

-Z'-X''-Y'-R_4,

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

-Z'-X''-R_5.

13. A compound of the Formula VI:



VI

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

p is an integer from 0 to 3;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;

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

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

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

or a pharmaceutically acceptable salt thereof.

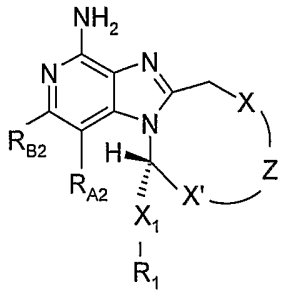
14. The compound or salt of claim 13 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of

alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

15. A compound of the Formula VII:



VII

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

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

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl; and

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

or a pharmaceutically acceptable salt thereof.

16. The compound or salt of claim 15 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups; and

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino,

heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino.

17. The compound or salt of claim 15 or 16 wherein R_{A2} and R_{B2} are each methyl.

18. The compound or salt of claim 7, 8, 9, or 10 wherein n is 0.

19. The compound or salt of claim 11, 12, 13, or 14 wherein p is 0.

20. The compound or salt of claim 7 or 8 wherein n and m are 0.

21. The compound or salt of claim 11 or 12 wherein p and m are 0.

22. The compound or salt of any one of claims 5, 6, 7, 8, 11, and 12 wherein R_3 is benzyloxy.

23. The compound or salt of any one of claims 5, 6, 7, 8, 11, 12, 18 as dependent on claim 7 or 8, and 19 as dependent on claim 11 or 12 wherein R_3 is -Z'-R_4.

24. The compound or salt of claim 23 wherein R_4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein alkyl and alkenyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, alkoxy, cyano, and aryl; wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, halogen, cyano, and dialkylamino; and wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

25. The compound or salt of claim 24 wherein Z' is -O-, and R_4 is alkynyl.

26. The compound or salt of claim 24 wherein Z' is a bond and R_4 is heterocyclyl which is selected from the group consisting of pyrrolidinyl, piperidinyl, oxazolidinyl,

morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

27. The compound or salt of claim 26 wherein -Z'-R_4 is 2-oxopyrrolidin-1-yl, morpholin-1-yl, or 2-oxo-1,3-oxazolidin-3-yl.

28. The compound or salt of any one of claims 1 through 14, or 22 wherein R is halogen or hydroxy.

29. The compound or salt of claim 7, 8, 11, or 12 wherein R is -$N(R_9)_2$ and m is 0.

30. The compound or salt of claim 29 wherein R is (cyclopropylmethyl)amino.

31. The compound or salt of any one of claims 5, 6, 7, 8, 11, 12, 18 as dependent on claim 7 or 8, and 19 as dependent on claim 11 or 12 wherein R_3 is -Z'-X"-R_4.

32. The compound or salt of claim 31 wherein X" is C_{1-3} alkylene or C_{1-3} alkenylene, and R_4 heterocyclyl or heteroaryl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo, and wherein heteroaryl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, cyano, and dialkylamino.

33. The compound or salt of claim 32 wherein R_4 is heterocyclyl which is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl and oxo.

34. The compound or salt of claim 32 wherein R_4 is heteroaryl which is selected from the group consisting of thiazolyl, imidazolyl, isoxazolyl, and pyridinyl each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, cyano, and dialkylamino.

35. The compound or salt of any one of claims 5, 6, 7, 8, 11, 12, 18 as dependent on claim 7 or 8, and 19 as dependent on claim 11 or 12 wherein R_3 is -Z'-X''-Y'-R_4.

36. The compound or salt of claim 35 wherein X'' is selected from the group consisting of C_{1-3} alkylene, C_{1-3} alkenylene, piperidin-1,4-diyl, and phenylene, Y' is selected from the group consisting of -$C(R_6)$-, -$C(R_6)$-O-, -$C(R_6)$-$N(R_8)$-, -$N(R_8)$-Q-, and -$S(O)_2$- wherein Q is selected from the group consisting of a bond, -C(O)-, -$S(O)_2$-, -and $C(R_6)$-$N(R_8)$-, R_6 is selected from the group consisting of =O and =S, and R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl; and

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and heterocyclyl; wherein alkyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, alkoxy, and aryl; wherein aryl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, halogen, cyano, dialkylamino, and alkoxy; and wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl and oxo.

37. The compound or salt of claim 36 wherein Y' is -$N(R_8)$-Q- wherein R_8 is hydrogen, Q is -$S(O)_2$-, -C(O)-, or -C(O)-NH-, and R_4 is C_{1-3} alkyl or pyridyl.

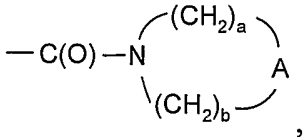
38. The compound or salt of claim 36 wherein Y' is -NH-$S(O)_2$- and R_4 is methyl, or Y' is -NH-C(O)- and R_4 is 3-pyridyl, or Y' is -C(O)-NH- and R_4 is hydrogen or C_{1-3} alkyl.

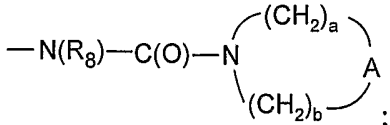
39. The compound or salt of claim 36 wherein Y' is -C(O)- and R_4 is heterocyclyl.

40. The compound or salt of claim 39 wherein heterocyclyl is selected from the group consisting of pyrrolidinyl, piperidinyl, thiazolidinyl, aziridinyl, azepanyl, diazepanyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and piperazinyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl and oxo.

41. The compound or salt of any one of claims 5, 6, 7, 8, 11, 12, 18 as dependent on claim 7 or 8, and 19 as dependent on claim 11 or 12 wherein R_3 is -Z'-X"-R_5.

42. The compound or salt of claim 41 wherein X" is selected from the group consisting of C_{1-3} alkylene and phenylene, and R_5 is selected from the group consisting of:



, and


; wherein A is -O-, -S-, or -SO_2-; R_8 is hydrogen or C_{1-4} alkyl; and a and b are each independently an integer of 1 to 3.

43. The compound or salt of claim 42 wherein A is -O-, and a and b are each 2.

44. The compound or salt of any one of claims 1 through 43 wherein Z is -N(-Y-R_2)-.

45. The compound or salt of any one of claims 1 through 43 wherein Z is -O-.

46. The compound or salt of any one of claims 1 through 44 wherein Y is selected from the group consisting of -C(O)-, -$S(O)_2$-, and -C(O)-NH-.

47. The compound or salt of claim 46 wherein Y is -$S(O)_2$- and R_2 is methyl.

48. The compound or salt of any one of claims 1 through 47 wherein R_1 is selected from the group consisting of alkyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, and alkoxy.

49. The compound or salt of claim 48 wherein R_1 is C_{1-3} alkyl optionally substituted by hydroxy or one or more fluorine atoms.

50. The compound or salt of claim 48 wherein R_1 is phenyl, benzyl, pyridinyl, or pyridinylmethyl, each of which is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, and alkoxy.

51. The compound or salt of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, and 17 through 47 except as dependent on claim 2, 4, 6, 8, 10, 12, 14, or 16 wherein R_1 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, halogen, hydroxy, aryl, heteroaryl, and heterocyclyl; and wherein when R_1 is heteroaryl, then the one or more substituents may also be independently selected from the group consisting of haloarylenyl, alkoxyarylenyl, alkylarylenyl, and arylalkylenyl; and wherein when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl and aminocarbonyl.

52. The compound or salt of claim 51 wherein R_1 is heterocyclyl which is selected from the group consisting of morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, thiazolidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, 1,3-dioxolanyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxyC_{1-4} alkyl, hydroxy, aminocarbonyl, arylC_{1-4} alkylenyl, and 5 to 7 membered heterocyclyl containing one or two heteroatoms.

53. The compound or salt of claim 51 wherein R_1 is heteroaryl which is selected from the group consisting of pyridyl, pyrazolyl, oxazolyl, and triazolyl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxyC_{1-4} alkyl, haloC_{1-4} alkyl, aryl, aryl substituted by fluoro, chloro, methyl, or methoxy, arylC_{1-4} alkylenyl, and heteroaryl.

54. The compound or salt of any one of claims 1 through 51 wherein R_1 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkenyl, and C_{1-4} alkynyl, each of which is

unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, and aryl.

55. The compound or salt of any one of claims 1 through 51 wherein R_1 is aryl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl, and hydroxyC_{1-4} alkyl.

56. The compound or salt of any one of claims 1 through 55 wherein X_1 is a bond or alkylene.

57 The compound or salt of claim 56 wherein X_1 is a bond.

58. The compound or salt of claim 56 wherein X_1 is $-CH_2-$.

59. The compound or salt of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, and 17 through 55 except as dependent on claim 2, 4, 6, 8, 10, 12, 14, or 16 wherein X_1 is C_{1-4} alkylene substituted by a hydroxy or methoxy group.

60. The compound or salt of any one of claims 1 through 55 wherein X_1 is C_{2-3} alkylene interrupted by one -O- group.

61. The compound or salt of claim 55 except as dependent on claim 2, 4, 6, 8, 10, 12, 14, or 16 wherein X_1 is C_{2-3} alkenylene or C_{2-3} alkynylene.

62. The compound or salt of any one of claims 1 through 61 wherein X is a bond.

63. The compound or salt of any one of claims 1 through 62 wherein X' contributes one ring carbon atom.

64. The compound or salt of any one of claims 1 through 63 wherein X' is C_{1-2} alkylene.

65. The compound or salt of claim 64 wherein X' is methylene.

66. The compound or salt of any one of claims 1 through 62 wherein X' contributes two ring carbon atoms.

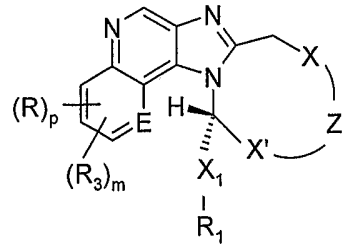
67. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 66 and a pharmaceutically acceptable carrier.

68. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 3 through 27, 28 except as dependent on claim 1 or 2, 29 through 43, and claims 44 through 66 except as dependent on claim 1 or 2 or administering the pharmaceutical composition of claim 67 comprising a compound or salt of any one of claims 3 through 27, 28 except as dependent on claim 1 or 2, 29 through 43, and claims 44 through 66 except as dependent on claim 1 or 2 to the animal.

69. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 3 through 27, 28 except as dependent on claim 1 or 2, 29 through 43, and claims 44 through 66 except as dependent on claim 1 or 2 or administering the pharmaceutical composition of claim 67 comprising a compound or salt of any one of claims 3 through 27, 28 except as dependent on claim 1 or 2, 29 through 43, and claims 44 through 66 except as dependent on claim 1 or 2 to the animal.

70. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 3 through 27, 28 except as dependent on claim 1 or 2, 29 through 43, and claims 44 through 66 except as dependent on claim 1 or 2 or administering the pharmaceutical composition of claim 67 comprising a compound or salt of any one of claims 3 through 27, 28 except as dependent on claim 1 or 2, 29 through 43, and claims 44 through 66 except as dependent on claim 1 or 2 to the animal.

71. A compound of the Formula X:



X

wherein:

E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and p is 0 or 1, and with the further proviso that when E is CR and m is 1, p is 0;

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_2)-;

X_1 is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and are optionally substituted by a hydroxy or methoxy group;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy;

heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_1 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

p is an integer from 0 to 3;

R_2 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; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

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

$-C(R_6)-$,

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

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

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

$-C(R_6)-O-$;

R_3 is selected from the group consisting of:

$-Y''-R_4$,

$-Z'-R_4$,

$-Z'-X''-R_4$,

$-Z'-X''-Y'-R_4$,

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

$-Z'-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

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;

Y' is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

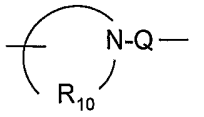
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

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

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

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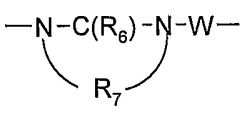
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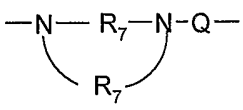
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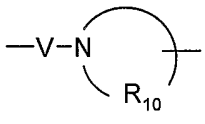
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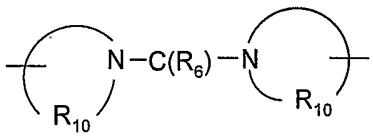
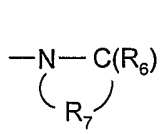

;

Y" is -O-C(R_6)-;

Z' is a bond or -O-;

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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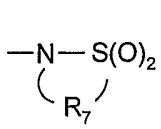
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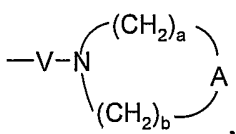
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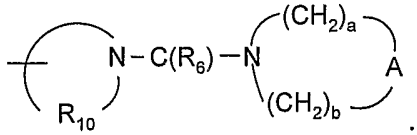
;

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, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

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 $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

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

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.

72. The compound or salt of claim 71 wherein:

X_1 is selected from the group consisting of a bond, alkylene, and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 is selected from the group consisting of 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; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; and, in the case of heterocyclyl, oxo; with the proviso that when R_1 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and

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.