ARYL / HETARYL SUBSTITUTED IMIDAZOQUINOLINES

FIELD OF THE INVENTION

This invention relates to derivatives of imidazoquinoline compounds and to pharmaceutical compositions containing the compounds. A further aspect of this invention relates to the use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases.

BACKGROUND OF THE INVENTION

The first reliable report on the 1H-imidazo[4,5-c]quinoline ring system, Backman et al., *J. Org. Chem.*, *15*, 1278-1284 (1950) describes the synthesis of 1-(6-methoxy-8-quinolinyl)-2-methyl-1H-imidazo[4,5-c]quinoline for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1H-imidazo[4,5-c] quinolines were reported. For example, Jain et al., *J. Med. Chem.*, *11*, 87-92 (1968), synthesized the compound 1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline as a possible anticonvulsant and cardiovascular agent. Also, Baranov et al., *Chem. Abs.*, *85*, 94362 (1976), have reported several 2-oxoimidazo[4,5-c]quinolines, and Berenyi et al., *J. Heterocyclic Chem.*, *18*, 1537-1540 (1981), have reported certain 2-oxoimidazo[4,5-c]quinolines.

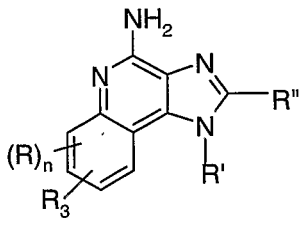
Certain 1H-imidazo[4,5-c]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. These are described in, inter alia, U.S.

Pat. Nos. 4,689,338; 4,698,348; 4,929,624; 5,037,986; 5,268,376; 5,346,905; and 5,389,640.

There continues to be interest in the imidazoquinoline ring system and there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

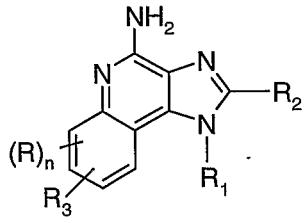
SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula (I):



I

and more specifically of the following Formula (II):



II

wherein: R, n, R', R", R_1, R_2, and R_3 are as defined below.

The compounds of Formulas I and II are useful 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. Compounds can be tested per the test procedures described in the Examples

Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human PBMC in a culture with the compound(s) at a concentration range of 30 to 0.014 μM and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. Compounds can be tested for inhibition of cytokine biosynthesis by incubating mouse macrophage cell line Raw 264.7 in a culture with the compound(s) at a single concentration of, for example, 5 μM and analyzing for tumor necrosis factor (α) in the culture supernatant. Compounds can be further tested for dose response by running the test at several compound concentrations, for example, 0.03, 0.1, 0.3, 1, 3, 5, and 10 μM. The ability to modulate cytokine biosynthesis makes the compounds useful in the treatment of a variety of conditions such as viral diseases, neoplastic diseases, and autoimmune diseases that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of modulating (e.g., inducing or inhibiting) cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic disease in an animal, by administering an effective amount of one or more compounds of Formula I (and more specifically, of Formula II) and/or pharmaceutically acceptable salts thereof to the animal.

In another aspect, the invention provides methods of synthesizing compounds of Formulas I and II and intermediates useful in the synthesis of these compounds.

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

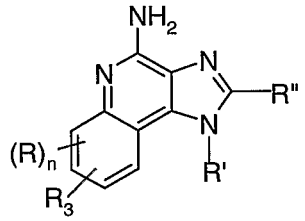
The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

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. Guidance is also provided herein through lists of examples, which 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 Formula (I):



I

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R' and R" are independently selected from the group consisting of hydrogen and non-interfering substitutents;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

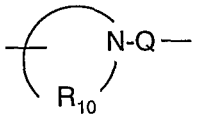
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

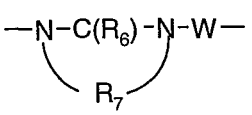
$-C(R_6)-N(R_8)-$,

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

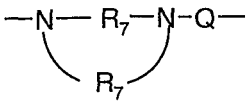
$-C(R_6)-N(OR_9)-$,



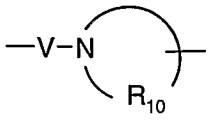
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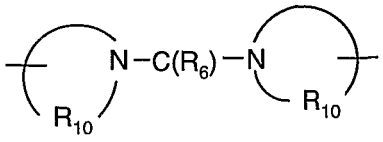
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, and

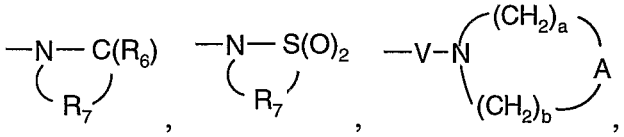


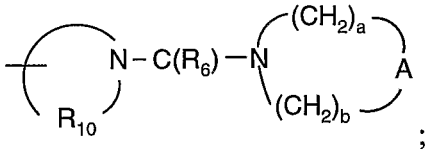
;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

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

R_5 is selected from the group consisting of:





and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_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.

For certain embodiments of Formula I, n is 0 and -Z- is a bond. For certain embodiments of Formula I, R_3 is -Z-Ar, and for certain other embodiments, R_3 is -Z-Ar'-Y-R_4 or -Z-Ar'-X-Y-R_4.

For some embodiments of Formula I, R' is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

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

-X-R_5;

wherein each X is independently selected, each Y is independently selected, each R_4 is independently selected, and each R_5 is independently selected.

For some embodiments of Formula I, R" is selected from the group consisting of:

-R_4,

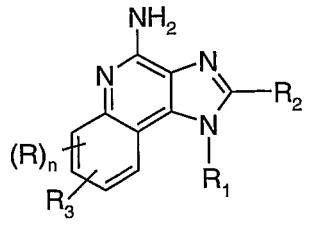
-X-R_4,

-X-Y-R_4, and

-X-R_5;

wherein each X is independently selected, each Y is independently selected, each R_4 is independently selected, and each R_5 is independently selected.

The present invention also provides compounds of the following Formula (II):



II

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

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

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$,

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

$-Z-Ar'-R_5$, and

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

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents

independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

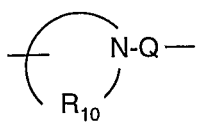
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

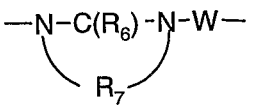
$-C(R_6)-N(R_8)-$,

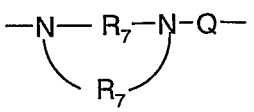
$-O-C(R_6)-N(R_8)-$,

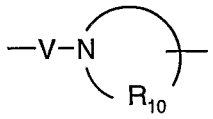
$-C(R_6)-N(OR_9)-$,

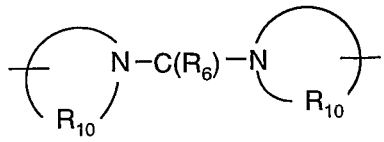


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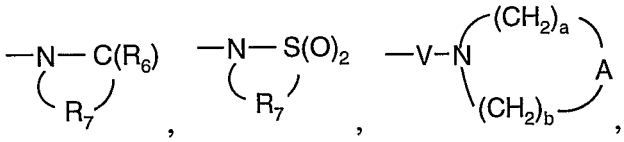

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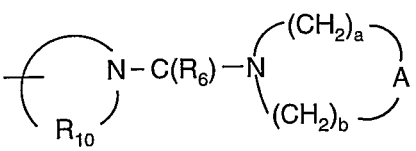

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:


,


and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

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

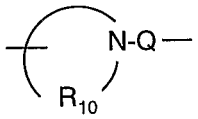
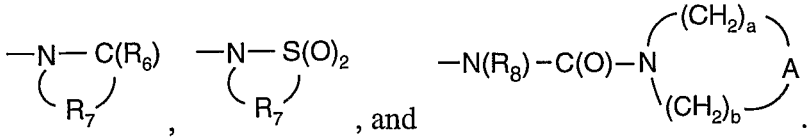
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

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 some embodiments of Formula II, R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X-Y-R_4, and -X-R_5; wherein X is alkylene; Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-C(O)-N(R_8)-$, and ; R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl; and R_5 is selected from the group consisting of .

In some embodiments of Formula II, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

For some embodiments of Formula II, n is 0 and -Z- is a bond. For some embodiments of Formula II, R_3 is -Z-Ar, and for certain of these embodiments, R_3 is selected from the group consisting of phenyl, pyridyl, pyrrolyl, thienyl, and furyl; each of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, carboxy, and cyano.

For some embodiments of Formula II, R_3 is -Z-Ar'-Y-R_4, -Z-Ar'-X-Y-R_4, or -Z-Ar'-R_5, and for certain of these embodiments, Ar' is phenyl or pyridyl;

Y is selected from the group consisting of:

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

-C(O)-,

-$N(R_8)$-Q-,

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

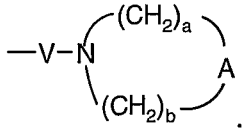
-$C(R_6)$-$N(OR_9)$-;

wherein Q is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-; R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and alkoxyalkylenyl;

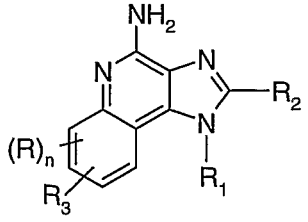
X is C_{1-4} alkylene;

R_4 is selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl; and

R_5 is



The present invention also provides compounds of the following Formula (IIa):



IIa

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

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

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar and

$-Z-Ar'-Y-R_4$;

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

each Y is independently selected from the group consisting of:

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

$-CR_6-$,

$-CR_6-O-$,

$-O-CR_6-$,

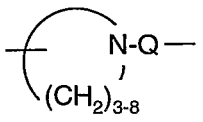
-O-C(O)-O-

$-NR_8-Q-$,

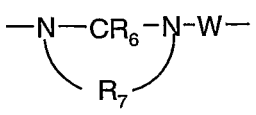
$-CR_6-NR_8-$,

-O-CR_6-NR_8-,

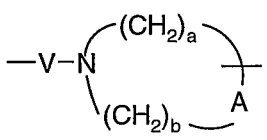
-CR_6-N(OR_9)-



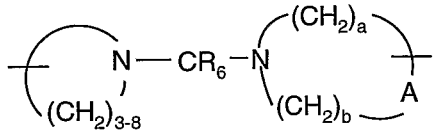
,



,



, and



;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

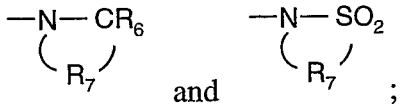
Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group

consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently 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;

each R_8 present is independently selected from the group consisting of hydrogen, alkyl, and arylalkyl;

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

A is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -NR_4-, and -CH_2-;

Q is selected from the group consisting of -CR_6-, -SO_2-, -CR_6-NR_8-W-, -SO_2-NR_8-, -CR_6-O-, and -CR_6-$N(OR_9)$-;

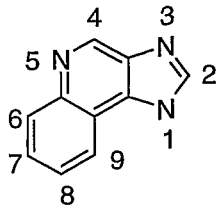
V is selected from the group consisting of –CR_6-, -O-CR_6-, and -NR_8-CR_6-;

W is selected from the group consisting of a bond, -C(O)-, and –SO_2-; and

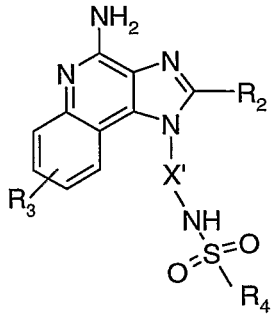
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

For certain embodiments of Formula IIa, n is 0 and the R_1, R_2, and R_3 groups are defined as follows: R_1 is R_4 or -X-Y-R_4, R_1 is alkyl or hydroxyalkyl, -X- is C_{2-6} alkylene, and -Y- is -$S(O)_{0-2}$- or -NR_8-Q-; R_2 is R_4 or R_2 is alkyl or alkoxyalkyl; R_3 is -Z-Ar, -Z- is a bond, -Ar is unsubstituted aryl or heteroaryl, and more particularly -Ar is phenyl, thienyl or pyridyl; and R_3 is attached at the 7-position or 8-position per the following numbering scheme.



The present invention also provides compounds of the following Formula (III), which include a sulfonamide functional group:



III

wherein:

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$,

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

$-Z-Ar'-R_5$, and

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

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl,

heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

X' is C_{2-8} alkylene;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

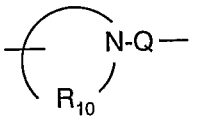
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

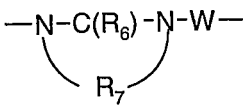
$-C(R_6)-N(R_8)-$,

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

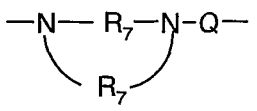
$-C(R_6)-N(OR_9)-$,

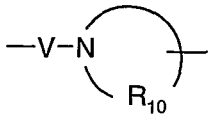


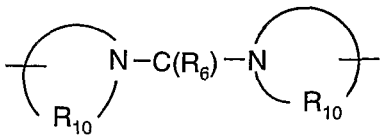
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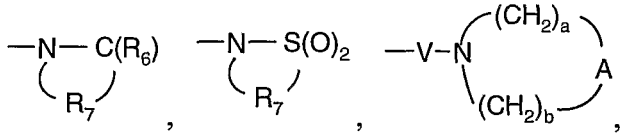

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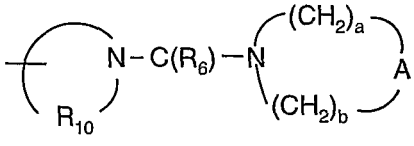

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:


,


and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, 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.

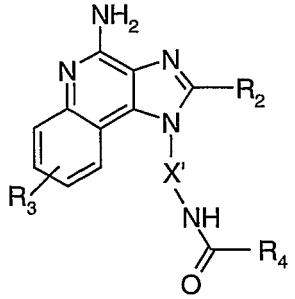
For certain embodiments of Formula III, X' is $-CH_2-C(CH_3)_2-$.

For certain embodiments of Formula III, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

For certain embodiments of Formula III, R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

For certain embodiments of Formula III, R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

The present invention also provides compounds of the following Formula (IV), which include an amide functional group:



IV

wherein R_2, R_3, R_4, and X' are the same as that for Formula III listed above; or a pharmaceutically acceptable salt thereof.

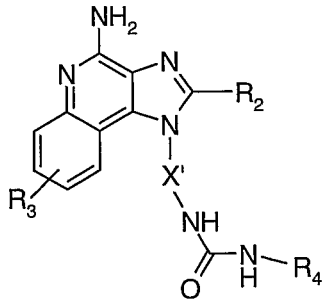
For certain embodiments of Formula IV, X' is $-CH_2-C(CH_3)_2-$.

For certain embodiments of Formula IV, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

For certain embodiments of Formula IV, R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

For certain embodiments of Formula IV, R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

The present invention also provides compounds of the following Formula (V), which include a urea functional group:



V

wherein R_2, R_3, R_4, and X' are the same as that for Formula III listed above; or a pharmaceutically acceptable salt thereof.

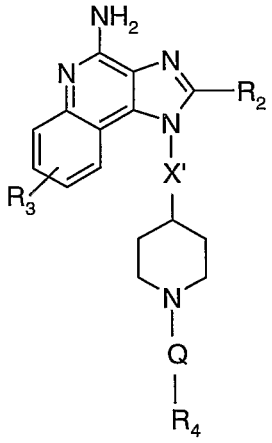
For certain embodiments of Formula V, X' is $-CH_2-C(CH_3)_2-$.

For certain embodiments of Formula V, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

For certain embodiments of Formula V, R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

For certain embodiments of Formula V, R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

The present invention also provides compounds of the following Formula (VI), which include a piperidine moiety:



VI

wherein R_2, R_3, R_4, Q, and X' are the same as that for Formula III listed above; or a pharmaceutically acceptable salt thereof.

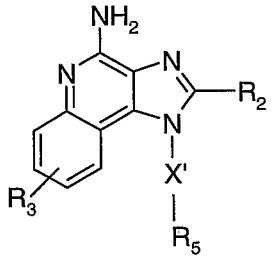
For certain embodiments of Formula VI, Q is selected from the group consisting of -C(O)-, $-S(O)_2-$, and -C(O)-NH-.

For certain embodiments of Formula VI, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

For certain embodiments of Formula VI, R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

For certain embodiments of Formula VI, R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

The present invention also provides compounds of the following Formula (VII):



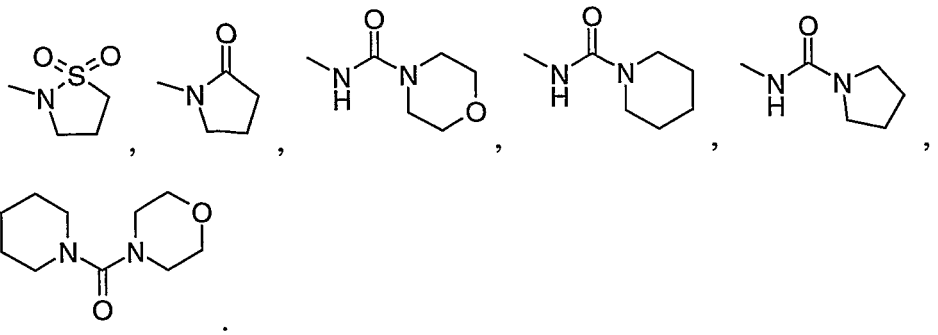
VII

wherein R_2, R_3, R_5, and X' are the same as that for Formula III listed above; or a pharmaceutically acceptable salt thereof.

For certain embodiments of Formula VII, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

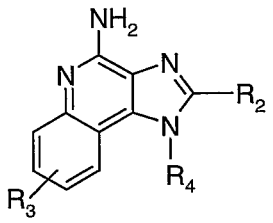
For certain embodiments of Formula VII, R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

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



and .

The present invention also provides compounds of the following Formula (VIII):



VIII

wherein R_2, R_3, and R_4 are the same as that for Formula III listed above; or a pharmaceutically acceptable salt thereof.

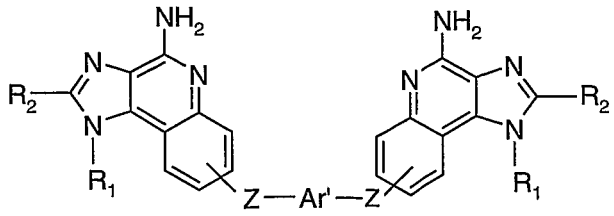
For certain embodiments of Formula VIII, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

For certain embodiments of Formula VIII, R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

For certain embodiments of Formula VIII, R_4 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-4} alkyl-O-C_{1-4} alkylenyl, and aryl-O-C_{1-4} alkylenyl.

For certain embodiments of Formula VIII, R_4 is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, 3-methoxypropyl, and phenoxyethyl.

The present invention also provides a compound of the following Formula (XLVI):



XLVI

wherein:

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

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

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

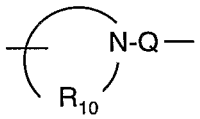
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

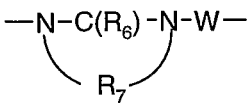
$-C(R_6)-N(R_8)-$,

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

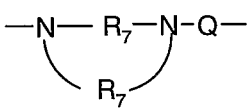
$-C(R_6)-N(OR_9)-$,



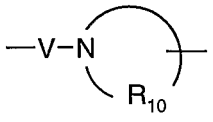
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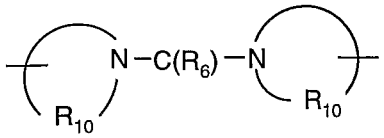
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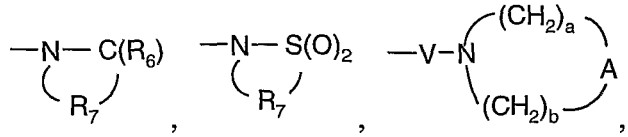
;

each Z is independently selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

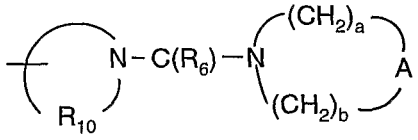
each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl,

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;

each R_5 is independently selected from the group consisting of:



and



;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, 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 $-S(O)_2$-;

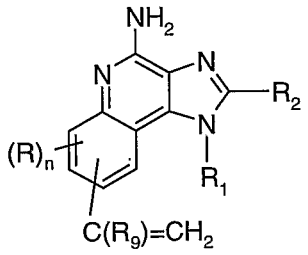
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

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

or a pharmaceutically acceptable salt thereof.

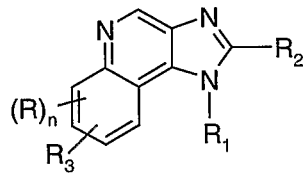
For certain embodiments of Formula XLVI, Z is a bond and Ar' is phenylene. For certain embodiments of Formula XLVI, R_1 is selected from the group consisting of alkyl, hydroxyalkyl, and -X-Y-R_4 wherein X is alkylene, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)-, and R_4 is alkyl. For certain embodiments of Formula XLVI, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

The present invention also provides compounds of the following Formulas XLVII and XLVIII, which are intermediates in the preparation of certain compounds of the present invention:



XLVII

and



XLVIII

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

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

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

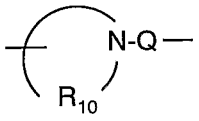
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

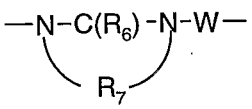
$-C(R_6)-N(R_8)-$,

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

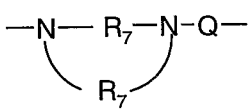
$-C(R_6)-N(OR_9)-$,



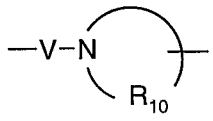
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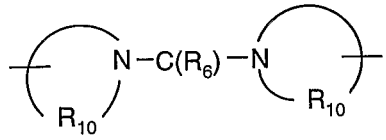
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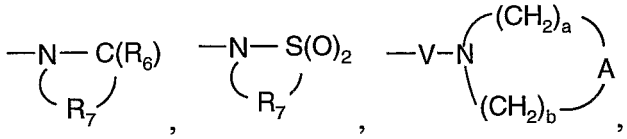
;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

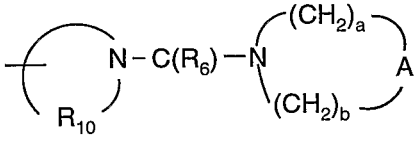
each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl,

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;

each R_5 is independently selected from the group consisting of:



,



and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, 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.

Herein, "non-interfering" means that the ability of the compound or salt to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R' groups include those described above for R_1 in Formula II. Illustrative non-interfering R" groups include those described above for R_2 in Formula II.

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, i.e. 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. Likewise, "alkylenyl," "alkenylenyl," and "alkynylenyl" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. 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.

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). Suitable 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. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, homopiperazinyl, and the like.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group is present more that once in a Formula I-VIII or XLVI-XLVIII described herein, each group is independently selected, whether specifically stated or not. For example, when more than one Y group is present in a Formula, each Y group is independently selected. Furthermore, subgroups contained within these groups are also independently selected. For example, when each Y group contains an R_6, each R_6 is also independently selected.

The invention is inclusive of the compounds and salts thereof, described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes

each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

In some embodiments, compounds of Formulas I-VIII and XLVI induce the biosynthesis of one or more cytokines.

In some embodiments, compounds of Formulas I-VIII and XLVI inhibit the biosynthesis of one or more cytokines.

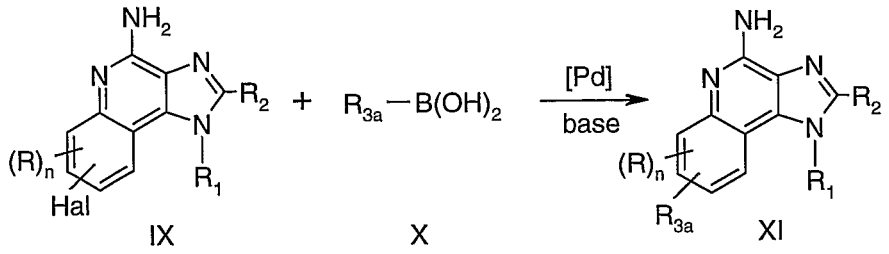
Preparation of the Compounds

Compounds of the invention can be prepared using known palladium catalyzed coupling reactions such as Suzuki coupling, Stille coupling, Sonogashira coupling, and the Heck reaction.

Suzuki coupling is used in Reaction Scheme I where R_1, R_2, and R are as defined above, R_{3a} is $-Z_a$-Ar, $-Z_a$-Ar'-Y-R_4, or $-Z_a$-Ar'-X-Y-R_4 where Z_a is a bond, alkylene or alkenylene, and Hal is bromo, chloro or iodo.

In Reaction Scheme I a halogen substituted imidazoquinoline of Formula IX is coupled with a boronic acid of Formula X to provide an imidazoquinoline of Formula XI which is a subgenus of Formula II. A compound of Formula IX is combined with a boronic acid of Formula X in the presence of palladium (II) acetate, triphenylphosphine and a base such as sodium carbonate in a suitable solvent such as n-propanol. The reaction can be carried out at an elevated temperature (e.g., 80-100°C).

Reaction Scheme I



Many compounds of Formula IX are known. See, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,268,376; 5,346,905; 5,389,640; 5,756,747; 6,331,539; and 6,451,810; PCT Publications WO 00/76518; WO 02/46188, WO

02/ 46189; WO 02/46190; WO 02/46191; WO 02/46192; and WO 02/46193; European Patent Application 1 104 764; and Japanese Patent Application 9-255926. Others can be readily prepared using known synthetic methods. See, for example, U.S. Patent Nos. 4,988,815; 5,175,296; 5,367,076; 5,395,937; and 5,741,908.

Many boronic acids of Formula X 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). The Suzuki coupling reaction can also be carried out using boronic acid esters of Formula R_{3a}-B(O-alkyl)$_2$ and anhydrides of boronic acids of Formula X.

Compounds of the invention where Z is alkynylene can be prepared using Stille coupling to couple a halogen substituted imidazoquinoline of Formula IX with a terminal alkyne of the formula -C≡C-Ar.

Compounds of the invention can be prepared according to Reaction Scheme II wherein R_b is selected from alkyl, and alkoxy; R_{1b} and R_{2b} are subsets of R_1 and R_2 as defined above, which subsets do not include those substituents which one skilled in the art would recognize as being susceptible to oxidation in step (9), examples include substituents containing an -S- or a heteroaryl group; R_{3b} is aryl which may be unsubstituted or substituted by one or more substituents independently selected from alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino; and n is 0 or 1.

In step (1) of Reaction Scheme II a bromoaniline of Formula XII is coupled with a boronic acid of formula R_{3b}-B(OH)$_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ using the method described in Reaction Scheme I to provide an aryl substituted aniline of Formula XIII. Many bromoanilines of Formula XII are commercially available; others can be readily prepared using known synthetic methods.

In step (2) of Reaction Scheme II an aryl substituted aniline of Formula XIII is reacted with a mixture of triethyl orthoformate and Meldrum's Acid (2,2-dimethyl-1,3-dioxane-4,6-dione) at an elevated temperature (50-55°C) to provide a compound of Formula XIV.

In step (3) of Reaction Scheme II a quinolin-4-ol of Formula XV is prepared by thermolysis of a compound of Formula XIV. The reaction can be carried out by heating (approximately 215°C) a solution of the compound of Formula XIV in a heat transfer fluid.

In step (4) of Reaction Scheme II a quinolin-4-ol of Formula XV is nitrated using conventional nitration methods to provide a 3-nitroquinolin-4-ol of Formula XVI. The reaction can be carried out by combining the compound of Formula XV with nitric acid in a suitable solvent such as propionic acid at an elevated temperature (approximately 130°C).

In step (5) of Reaction Scheme II a 3-nitroquinolin-4-ol of Formula XVI is chlorinated using conventional chlorinating methods to provide a 4-chloro-3-nitroquinoline of Formula XVII. The reaction can be carried out by combining the compound of Formula XVI with phosphorous oxychloride in a suitable solvent such as toluene. The reaction can be carried out at ambient temperature.

In step (6) of Reaction Scheme II a 4-chloro-3-nitroquinoline of Formula XVII is reacted with an amine of Formula R_{1b}-NH_2 to provide a 3-nitroquinolin-4-amine of Formula XVIII. The reaction can be carried out by adding the amine to a solution of the compound of Formula XVII in a suitable solvent such as *N,N*-dimethylformamide (DMF) in the presence of a tertiary amine such as triethylamine. The addition can be carried out at a reduced temperature (0°C) or at ambient temperature.

In step (7) of Reaction Scheme II a 3-nitroquinolin-4-amine of Formula XVIII is reduced to provide a quinoline-3,4-diamine of Formula XIX. The reaction can be carried out using a conventional heterogeneous hydrogenation catalyst such as platinum on carbon or palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as toluene, isopropanol, or mixtures thereof.

Alternatively the reduction in step (7) can be carried out using sodium dithionite. A solution or suspension of the compound of Formula XVIII in a suitable solvent such as ethanol or isopropanol is treated with an aqueous solution of sodium dithionite. The reaction can be carried out at an elevated temperature (reflux) or at ambient temperature.

In step (8) of Reaction Scheme II a quinoline-3,4-diamine of Formula XIX is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XX. Suitable equivalents to carboxylic acid include orthoesters, and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired R_{2b} substituent in a compound of Formula XX. For example, triethyl orthoformate will provide a compound where R_{2b} is hydrogen and trimethyl orthovalerate will provide a compound where R_{2b} is butyl. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included.

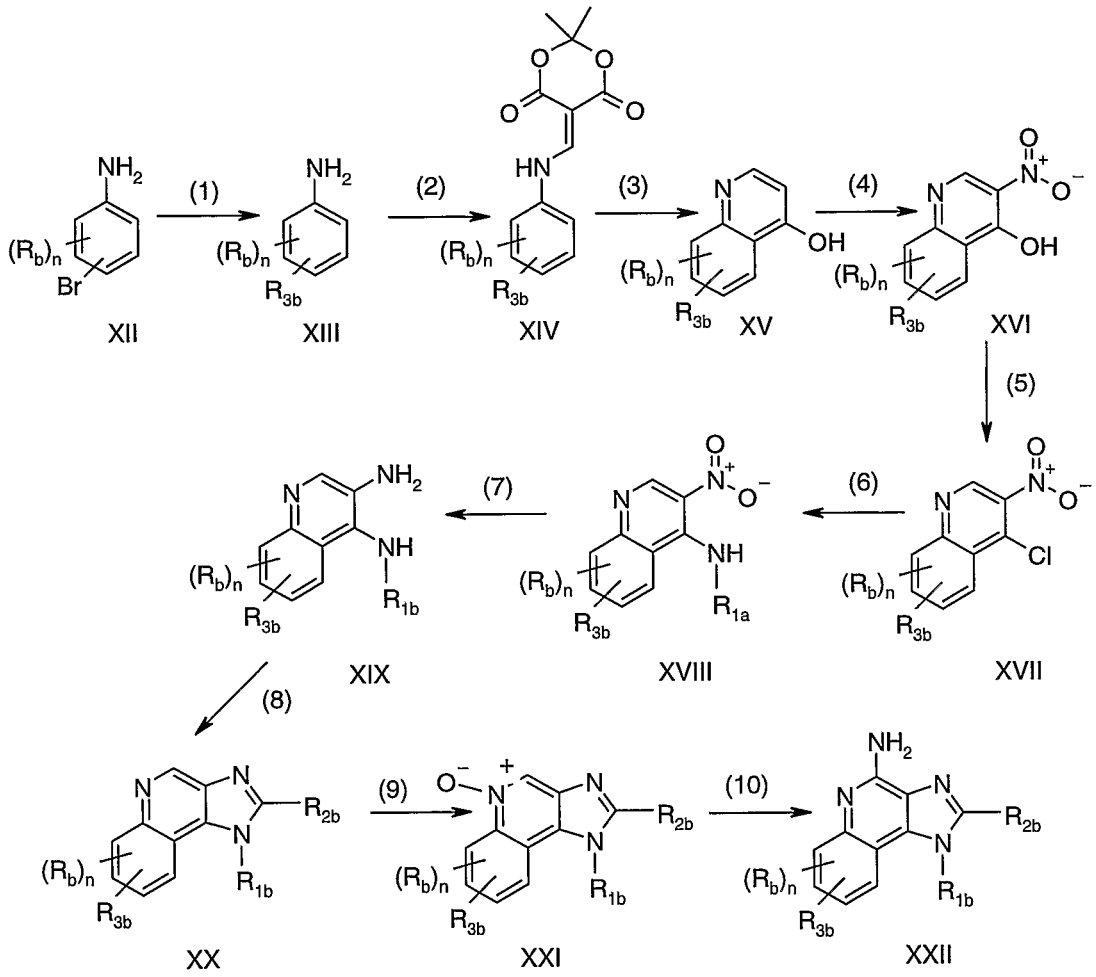
Alternatively, step (8) can be carried out by (i) reacting a compound of Formula XIX with an acyl halide of formula $R_{2b}C(O)Cl$ or $R_{2b}C(O)Br$ and then (ii) cyclizing. In part (i) the acyl halide is added to a solution of a compound of Formula XIX in an inert solvent such as acetonitrile, pyridine or dichloromethane. The reaction can be carried out at ambient temperature. Optionally a catalyst such as pyridine hydrochloride can be included. In part (ii) the product of part (i) is heated in pyridine. If step (i) is run in pyridine, then the two steps can be combined into a single step.

In step (9) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinoline of Formula XX is oxidized to provide an N-oxide of Formula XXI using a conventional oxidizing agent that is capable of forming N-oxides. The reaction can be carried out by treating a solution of a compound of Formula XX in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature.

In step (10) of Reaction Scheme II an N-oxide of Formula XXI is aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXII which is a subgenus of Formula II. The reaction is carried out in two parts. In part (i) a compound of Formula XXI is reacted with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chorides (e.g., benzenesulfonyl choride, methanesulfonyl choride, and *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable

aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a compound of Formula XXI in a suitable solvent such as dichloromethane or chloroform, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

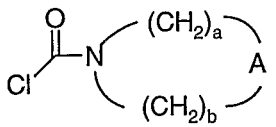
Reaction Scheme II



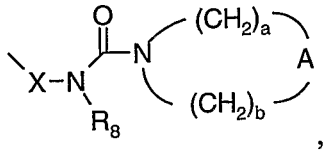
For some embodiments, compounds shown in Reaction Scheme II can be further elaborated using conventional synthetic methods. For example, an amine of Formula R_{1b}-NH_2, where R_{1b} is R_{4b} and R_{4b} is a subset of R_4 that does not include those substitutents which one skilled in the art would recognize as being

susceptible to oxidation in step (9), may be substituted by a hydroxy or second amino group, which can be further functionalized before step (7) of Reaction Scheme II. For example, a 3-nitroquinolin-4-amine of Formula XVIII, in which R_{1b} is R_{4b} having an amino substituent, can react with an acid chloride of Formula $R_{4b}C(O)Cl$, a sulfonyl chloride of Formula $R_{4b}S(O)_2Cl$, or a sulfonic anhydride of Formula $(R_{4b}S(O)_2)_2O$ to provide a compound of Formula XVIII in which R_{1b} is -X-Y-R_{4b}, where Y is -N(R_8)-Q-, R_8 is as defined above, and Q is -C(O)- or -SO_2-. Numerous acid chlorides, sulfonyl chlorides, and sulfonic anhydrides are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding an acid chloride of Formula $R_{4b}C(O)Cl$, a sulfonyl chloride of Formula $R_{4b}S(O)_2Cl$, or a sulfonic anhydride of Formula $(R_{4b}S(O)_2)_2O$ to a solution of a 3-nitroquinolin-4-amine of Formula XVIII, in which R_{1b} is R_{4b} having an amino substituent, and a base such as triethylamine in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature.

A 3-nitroquinolin-4-amine of Formula XVIII, in which R_{1b} is R_{4b} having an amino substituent, can also react with isocyanates of Formula $R_{4b}N=C=O$ to provide a compound of Formula XVIII in which R_{1b} is -X-Y-R_{4b}, where Y is -N(R_8)-Q-, R_8 is as defined above, and Q is -C(R_6)-N(R_8)-W-, R_6 is =O, and W is a bond. Numerous isocyanates of Formula $R_{4b}N=C=O$ 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 $R_{4b}N=C=O$ to a solution of the 3-nitroquinolin-4-amine of Formula XVIII, in which R_{1b} is R_{4b} having an amino substituent, in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature. Alternatively, a compound of Formula XVIII can be treated with an isocyanate of Formula $R_{4b}(CO)N=C=O$, a thioisocyanate of Formula $R_{4b}N=C=S$, a sulfonyl isocyanate of Formula $R_{4b}S(O)_2N=C=O$, or a carbamoyl chloride of Formula $R_{4b}N$-(R_8)-C(O)Cl or



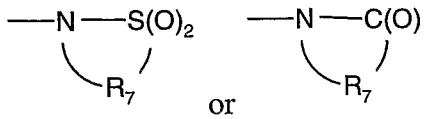
to provide a compound of Formula XVIII, where R_{1b} is -X-N(R_8)-Q-R_{4b} or



,

Q is -C(R_6)-N(R_8)-W-, and R_6, R_8, and W are as defined above. The product can then be treated according to steps (7) through (10) of Reaction Scheme II to provide 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXII.

Compounds of the invention, where R_{1c} is -X-Y-R_{4b} or -X-R_5; Y is -N(R_8)-Q-; R_5 is



; and X, Q, R, R_2, R_{3a}, R_{4b}, and n are as defined above can be prepared according to Reaction Scheme III. Steps (1) through (4) of Reaction Scheme III are carried out as described for steps (2) through (5) of Reaction Scheme II.

In step (5) of Reaction Scheme III, a 4-chloro-3-nitroquinoline of Formula XXVII is treated with a Boc-protected diamine of Formula $(CH_3)_3CO$-C(O)-NH-X-NH_2 to provide a protected 3-nitroquinolin-4-amine of Formula XXVIII. Several Boc-protected diamines of Formula $(CH_3)_3CO$-C(O)-NH-X-NH_2 are commercially available; others can be prepared by known synthetic methods. The reaction is conveniently carried out by adding a solution of the Boc-protected diamine of Formula $(CH_3)_3CO$-C(O)-NH-X-NH_2 to a cooled solution of a 4-chloro-3-nitroquinoline of Formula XXVII 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, and the product can be isolated using conventional methods.

In steps (6) and (7) of Reaction Scheme III, a 3-nitroquinolin-4-amine of Formula XXVIII is first reduced to provide a quinoline-3,4-diamine of Formula XXIX, which is converted to 1*H*-imidazo[4,5-*c*]quinoline of Formula XXX by reaction with a carboxylic acid equivalent. Steps (6) and (7) of Reaction Scheme III can be carried out as described for steps (7) and (8) of Reaction Scheme II. The sodium dithionite reduction in step (6) can also be conveniently carried out in a mixture of dichloromethane and water at ambient temperature in the presence of potassium carbonate and 1,1'-di-*n*-octyl-4,4'-bipyridinium

dibromide. In part (ii) of step (7), the cyclization can also be carried out in ethanol while heated at reflux.

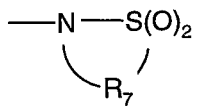
In step (8) of Reaction Scheme III, the Boc-protecting group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXX is removed to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXI. The reaction is conveniently carried out by adding hydrochloric acid or a solution of hydrochloric acid in ethanol to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXX in a suitable solvent such as ethanol. The reaction can be carried out at an elevated temperature, for example, the reflux temperature of the solvent. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (9) of Reaction Scheme III, an amino-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXI is converted to a 1*H*-imidazo[4,5-*c*]quinolin-1-yl compound of Formula XXXII, where R_{1c} is as defined above, using conventional methods. For example, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXI can react with an acid chloride of Formula $R_{4b}C(O)Cl$ to provide a compound of Formula XXXII in which R_{1c} is $-X-Y-R_{4b}$, Y is $-N(R_8)-Q-$, and Q is -C(O)-. In addition, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXI can react with sulfonyl chloride of Formula $R_{4b}S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_{4b}S(O)_2)_2O$ to provide a compound of Formula XXXII in which R_{1c} is $-X-Y-R_{4b}$, Y is $-N(R_8)-Q-$, and Q is $-S(O)_2-$. Numerous acid chlorides of Formula $R_{4b}C(O)Cl$, sulfonyl chlorides of Formula $R_{4b}S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_{4b}S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out as described above for a compound of Formula XVIII.

Ureas of Formula XXXII, where R_{1c} is $-X-Y-R_{4b}$, Y is $-N(R_8)-Q-$, Q is $-C(R_6)-N(R_8)-W-$, and W and R_8 are as defined above can be prepared by reacting a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXI with isocyanates of Formula $R_4N=C=O$ or Formula $R_4(CO)N=C=O$, thioisocyanates of Formula $R_4N=C=S$, sulfonyl isocyanates of Formula $R_4S(O)_2N=C=O$, or carbamoyl chlorides of Formula $R_4N-(R_8)-C(O)Cl$. Numerous compounds of these types are commercially available; others can be readily prepared using known

synthetic methods. The reaction can be carried out as described above for a compound of Formula XVIII.

Compounds of Formula XXXII where R_{1c} is -X-R_5 and R_5 is

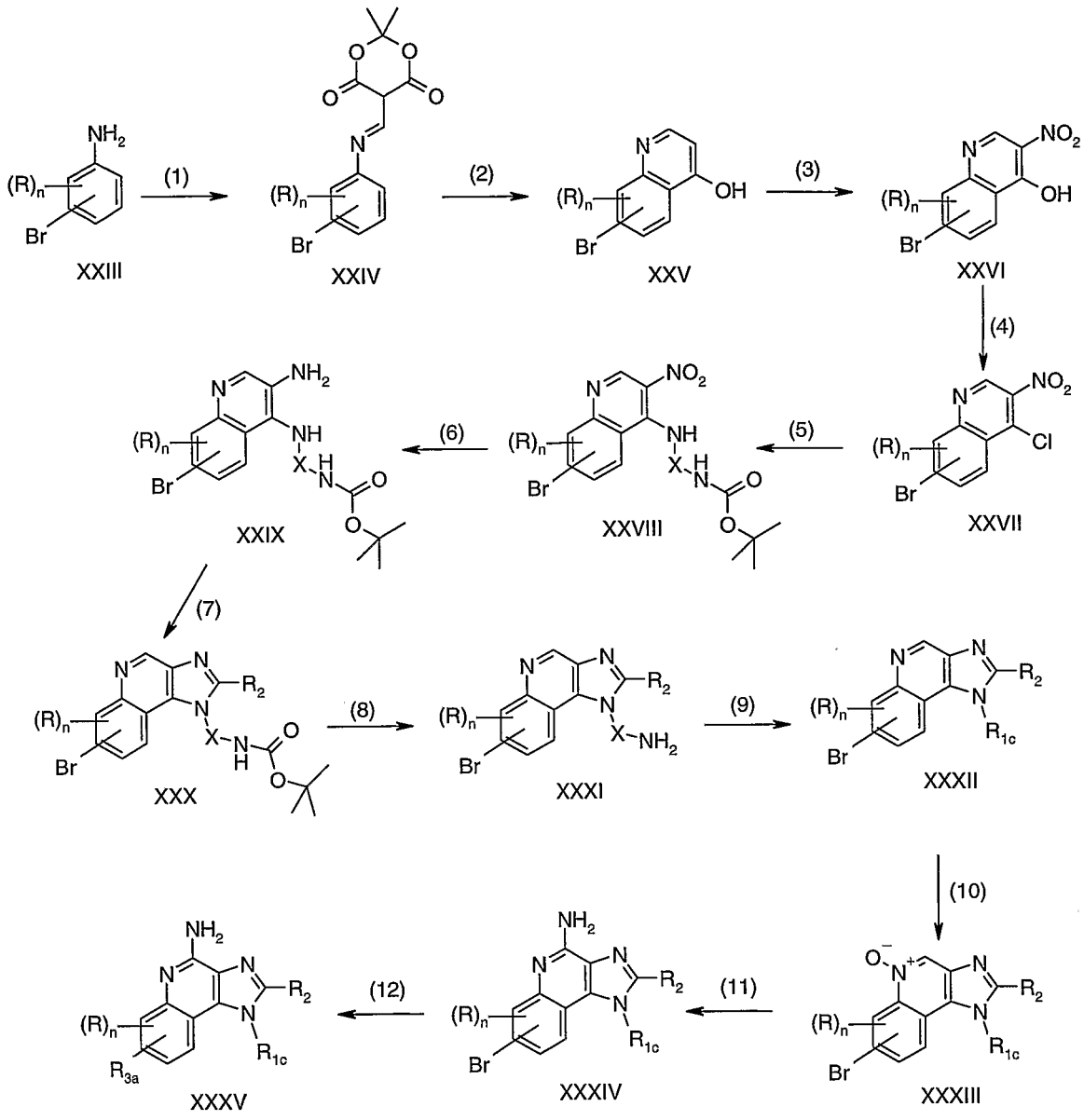


can be prepared by treating an amino-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXI with a chloroalkanesulfonyl chloride of Formula Cl-$R_7S(O)_2Cl$. The reaction is conveniently carried out by adding the chloroalkanesulfonyl chloride to a solution of the amino-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXI in a suitable solvent such as chloroform at ambient temperature. The isolable intermediate chloroalkanesulfonamide can then be treated with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene at ambient temperature in a suitable solvent such as DMF to effect the cyclization. The product can be isolated using conventional methods.

In steps (10) and (11) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXII is oxidized to afford a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXXIII, which is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXIV. Steps (10) and (11) of Reaction Scheme III can be carried out as described for steps (9) and (10), respectively, of Reaction Scheme II.

In step (12) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXIV undergoes a coupling reaction with boronic acid of Formula X, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$. The Suzuki coupling reaction can be carried out as described in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXV, which is a subgenus of Formula II. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III



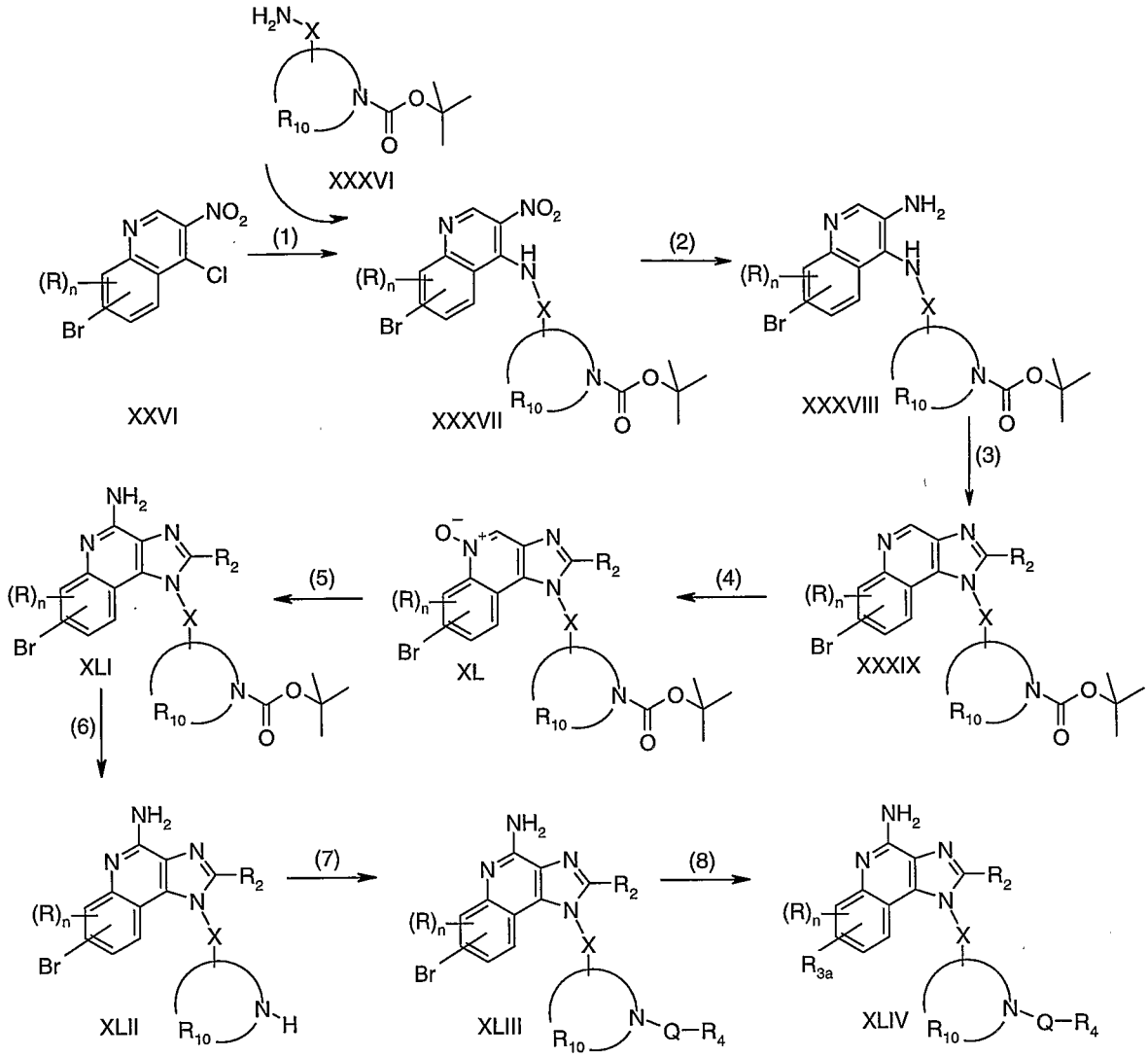
Compounds of the invention can also be prepared according to Reaction Scheme IV, where R, R_2, R_{3a}, R_4, R_{10}, X, and Q are as defined above. In step (1) of Reaction Scheme IV, a 4-chloro-3-nitroquinoline of Formula XXVII is treated with a Boc-protected diamine of Formula XXXVI to provide a 3-nitroquinolin-4-amine of Formula XXXVII. Boc-protected diamines of Formula XXXVII are available from the method described by Carceller, E. et al, *J. Med. Chem.*, *39*, 487-493 (1996). The reaction can be carried out as described for step (5) of Reaction Scheme III.

In steps (2)-(5) of Reaction Scheme IV, a 3-nitroquinolin-4-amine of Formula XXXVII is first reduced to provide a quinoline-3,4-diamine of Formula XXXVIII, which is converted to 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXIX by reaction with a carboxylic acid equivalent. The 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXIX is then oxidized to afford a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XL, which is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XLI. Steps (2), (3), (4), and (5) of Reaction Scheme IV can be carried out as described for steps (7), (8), (9), and (10), respectively, of Reaction Scheme II.

In steps (6) of Reaction Scheme IV, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XLI is removed to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XLII, which is converted to a 1*H*-imidazo[4,5-*c*]quinolinyl compound of Formula XLIII in step (7). Steps (6) and (7) of Reaction Scheme IV can be carried out as described for steps (8) and (9) of Reaction Scheme III.

In step (8), the compound of Formula XLIII is then coupled with a boronic acid of Formula X, an anhydride thereof, or boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XLIV, which is a subgenus of Formula II. The Suzuki coupling reaction can be carried out as described in Reaction Scheme I. In some embodiments, the coupling reaction shown in step (8) is carried out prior to the deprotection and functionalization reactions shown in steps (6) and (7) to provide a compound of Formula XLIV. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IV

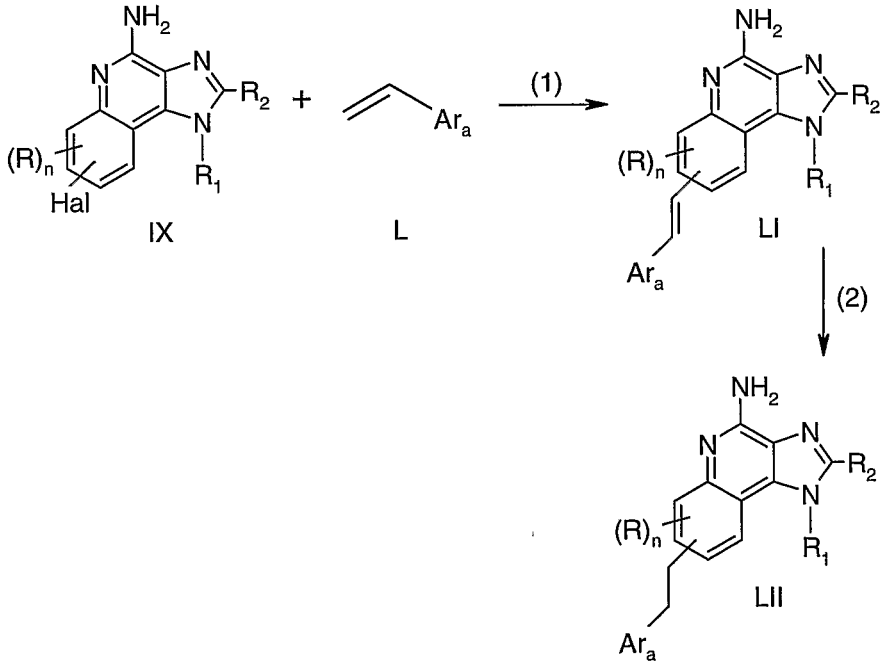


The Heck reaction can be used to prepare compounds of the invention as shown in step (1) of Reaction Scheme V, wherein R_1, R_2, R, Hal, and n are as defined above and Ar_a is -Ar, -Ar'-Y-R_4, or -Ar'-X-Y-R_4. In step (1) of Reaction Scheme V, a halogen-substituted imidazoquinolin-4-amine of Formula IX is coupled with a vinyl-substituted compound of Formula L to provide an imidazoquinolin-4-amine of Formula LI, which is a subgenus of Formula II. Alternatively, a compound of Formula L can be coupled with a trifluoromethanesulfonate-substituted imidazoquinolin-4-amine, in which Hal in Formula IX is replaced by -OSO_2CF_3. Several compounds of Formula L are commercially available; others can be prepared by known methods. The reaction is conveniently carried out by combining the imidazoquinolin-4-amine

of Formula IX and the vinyl-substituted compound of Formula L in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base such as triethylamine in a suitable solvent such as acetonitrile or toluene. The reaction can be carried out at an elevated temperature such as 100-120 °C under an inert atmosphere. The compound or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2) of Reaction Scheme V, the vinyl group of an imidazoquinolin-4-amine of Formula LI is reduced to provide an imidazoquinolin-4-amine of Formula LII, which is also a subgenus of Formula II. 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. The compound or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme V



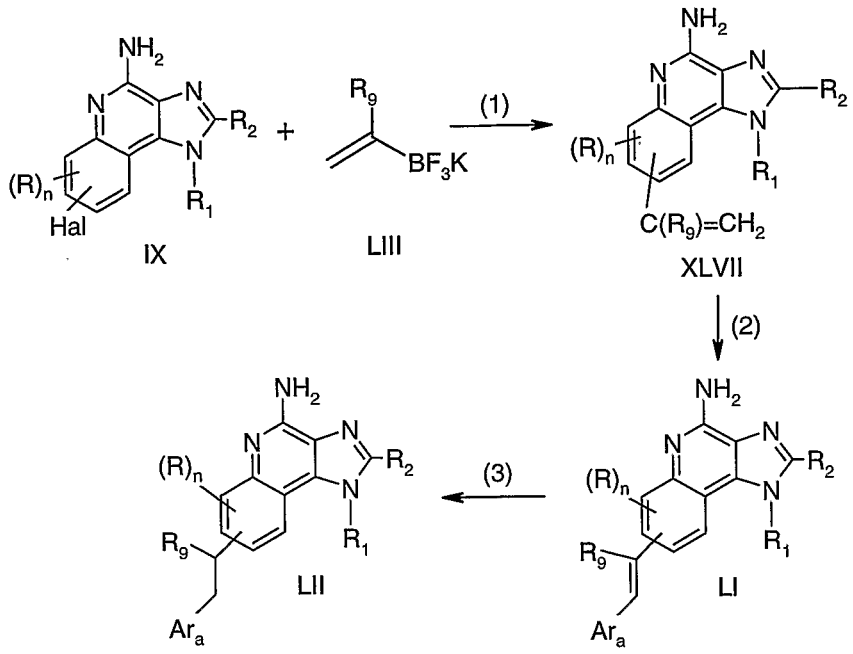
Palladium-catalyzed coupling reactions can also be used to prepare compounds of the invention according to Reaction Scheme VI, wherein R_1, R_2, R_9, R, Hal, Ar_a, and n are as defined above. In step (1) of Reaction Scheme VI, a halogen-substituted imidazoquinolin-4-amine of Formula IX undergoes a

Suzuki-type coupling with a potassium alkenyltrifluoroborate of Formula LIII to provide an imidazoquinolin-4-amine of Formula XLVII. The reaction is conveniently carried out by combining the imidazoquinolin-4-amine of Formula IX and a compound of Formula LIII, such as potassium vinyltrifluoroborate, in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct and a base such as triethylamine in a suitable solvent such as *n*-propanol. The reaction can be carried out at an elevated temperature such as the reflux temperature of the solvent under an inert atmosphere. The compound or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2) of Reaction Scheme VI, the Heck reaction is used to couple a vinylated imidazoquinolin-4-amine of Formula XLVII with an aryl or hetereoaryl halide of Formula Ar_a-Hal or a trifluoromethanesulfonate of Formula Ar_a-OSO_2CF_3. Numerous compounds of Formula Ar_a-Hal are commercially available; others can be prepared using known synthetic methods. The reaction is conveniently carried out under the conditions described in step (1) of Reaction Scheme V to provide an imidazoquinolin-4-amine of Formula LI. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

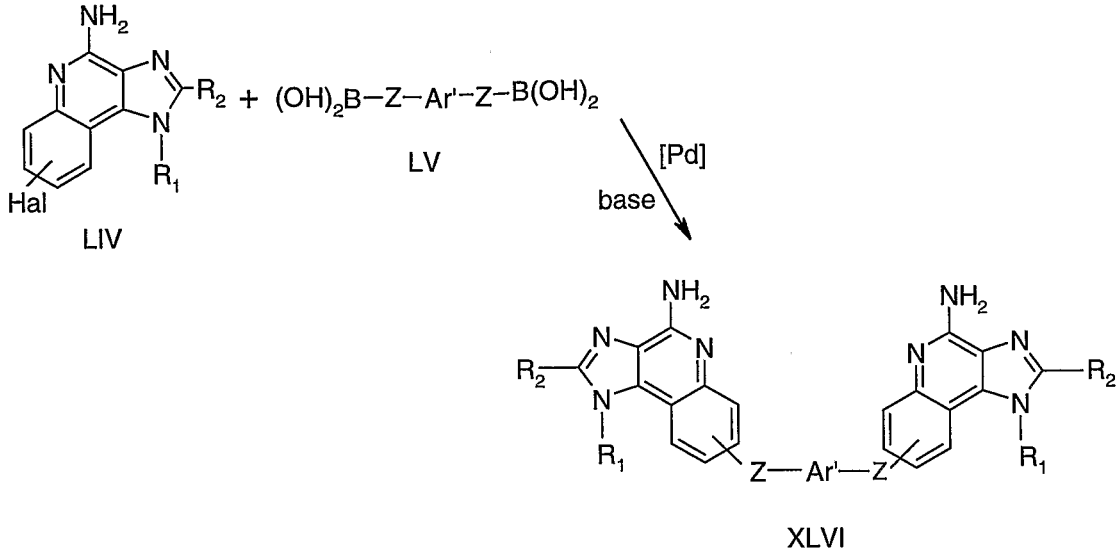
In step (3) of Reaction Scheme VI, the vinyl group of an imidazoquinolin-4-amine of Formula LI is reduced to provide an imidazoquinolin-4-amine of Formula LII. The reaction is conveniently carried out by hydrogenation under the conditions described in step (2) of Reaction Scheme V.

Reaction Scheme VI



Dimers of the invention can be prepared according to Reaction Scheme VII, wherein R_1, R_2, Z, Hal, and Ar' are as defined above. In Reaction Scheme VII, a Suzuki coupling is carried out with an imidazoquinolin-4-amine of Formula LIV and a difunctional boronic acid of Formula LV, or an ester or anhydride thereof. Some boronic acids of Formula LV are commercially available; others can be prepared by known synthetic methods. The coupling can be carried out as described in Reaction Scheme I to provide a dimer of Formula XLVI. The compound or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VII



XLVI

Compounds of the invention can also be prepared according to Reaction Scheme VIII, wherein R, R_{3a}, n, and Hal are as defined above, and R_{1d} and R_{2d} are subsets of R_1 and R_2 that do not include substituents that one skilled in the art would recognize as being susceptible to nucleophilic attack in step (5). These groups include, for example, esters and ureas. In step (1) of Reaction Scheme VIII, a nitro-substituted quinoline-2,4-diol of Formula LVI is chlorinated to provide a 2,4-dichloroquinoline of Formula LVII. Nitro-substituted quinoline-2,4-diols of Formula LVI can be prepared from substituted anilines according to the methods described in Buckle *et al*, *J. Med. Chem.*, *18*, 726-732 (1975). The chlorination is conveniently carried out by heating the compound of Formula LVI and phenylphosphonic dichloride at an elevated temperature such as 140 °C. The reaction can be carried out without solvent, and the product can be isolated using conventional methods.

In step (2) of Reaction Scheme VIII, a 2,4-dichloroquinoline of Formula LVII is reacted with an amine of Formula R_1-NH_2 to provide a 2-chloro-3-nitroquinolin-4-amine of Formula LVIII. The reaction can be carried out as described in step (6) of Reaction Scheme II.

In step (3) of Reaction Scheme VIII, the nitro group of a 2-chloro-3-nitroquinolin-4-amine of Formula LVIII is reduced to provide a 2-chloroquinoline-3,4-diamine of Formula LIX. The reduction is conveniently

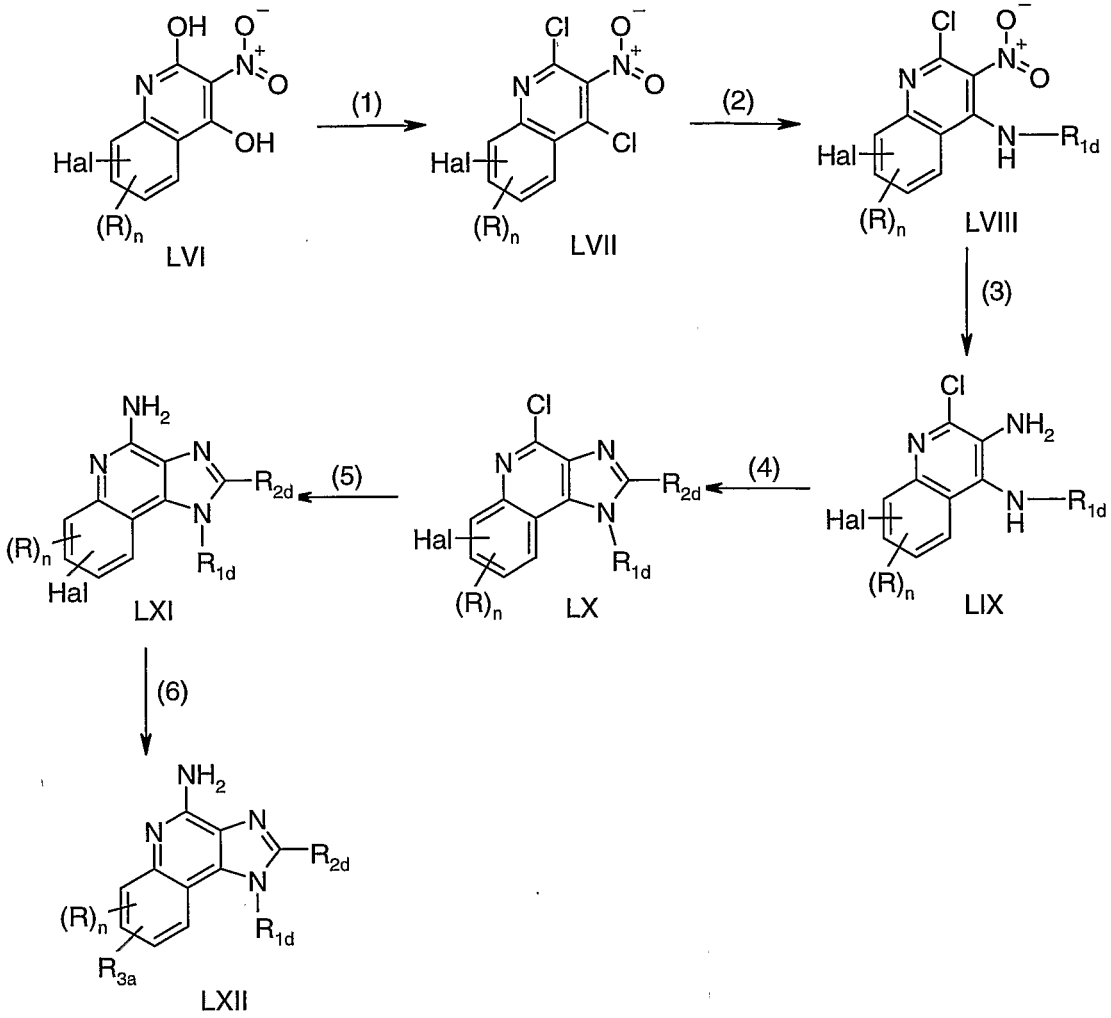
carried out with sodium dithionite according to the method described in step (7) of Reaction Scheme II.

In step (4) of Reaction Scheme VIII, a 2-chloroquinoline-3,4-diamine of Formula LIX is treated with a carboxylic acid or an equivalent thereof to provide a 4-chloro-1*H*-imidazo[4,5-*c*]quinoline of Formula LX. The reaction can be carried out as described in step (8) of Reaction Scheme II.

In step (5) of Reaction Scheme VIII, a 4-chloro-1*H*-imidazo[4,5-*c*]quinoline of Formula LX is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXI. The reaction is conveniently carried out by combining the compound of Formula LX with a solution of ammonia in methanol in a bomb reactor and heating at an elevated temperature, such as 120 °C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme VIII, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXI undergoes a coupling reaction with a boronic acid of Formula X, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$. The Suzuki coupling reaction can be carried out as described in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXII, which is a subgenus of Formula II. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VIII



For some embodiments, compounds of the invention are prepared according to Reaction Scheme IX, where R, R_2, R_{3a}, R_4, X, Q, and n are as defined above. In step (1) of Reaction Scheme IX, a 4-chloro-3-nitroquinoline of Formula XXVII is treated with a Boc-protected piperazine of Formula LXIII to provide a 3-nitroquinolin-4-amine of Formula LXIV. The reaction can be carried out as described for step (5) of Reaction Scheme III.

In steps (2) and (3) of Reaction Scheme IX, a 3-nitroquinolin-4-amine of Formula LXIV is first reduced to provide a quinoline-3,4-diamine of Formula LXV, which is converted to 1*H*-imidazo[4,5-*c*]quinoline of Formula LXVI by reaction with a carboxylic acid equivalent. Step (2) of Reaction Scheme IX can be carried out as described for step (7) of Reaction Scheme II or step (8) of

Reaction Scheme III. Step (3) of Reaction Scheme IX can be carried out as described for step (8) of Reaction Scheme II.

The 1*H*-imidazo[4,5-*c*]quinoline of Formula LXVI is then oxidized in step (4) of Reaction Scheme IX to afford a dioxido-1*H*-imidazo[4,5-*c*]quinoline of Formula LXVII. The oxidation reaction is conveniently carried out in a similar manner to step (9) of Reaction Scheme II but with additional equivalents of 3-chloroperoxybenzoic acid. The product can be isolated using conventional methods.

In step (5) of Reaction Scheme IX, a dioxido-1*H*-imidazo[4,5-*c*]quinoline of Formula LXVII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXVIII. Step (5) of Reaction Scheme IX can be carried out as described for step (10) of Reaction Scheme II.

In step (6) of Reaction Scheme IX, the piperazine *N*-oxide of the 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXVIII is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXIX. The reaction is conveniently carried out by adding phosphorous trichloride to an *N*-oxide of Formula LXVIII in a suitable solvent such as chloroform. The reaction can be carried out at a subambient temperature, such as 4 °C. The product can be isolated using conventional methods.

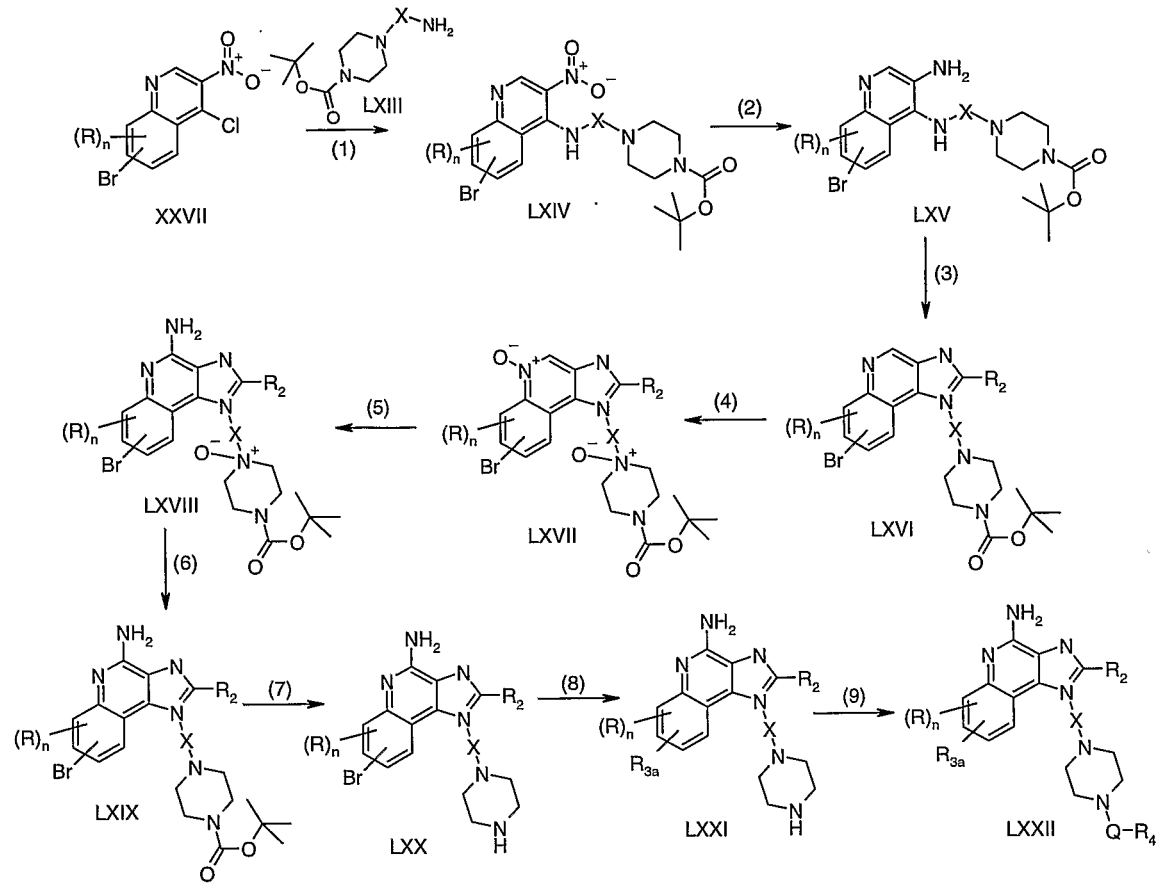
In step (7) of Reaction Scheme IX, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXIX is removed to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXX. The deprotection can be carried out as described in step (8) of Reaction Scheme III.

In step (8) of Reaction Scheme IX, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXX is coupled with a boronic acid of Formula X, an anhydride thereof, or boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXXI, which is a subgenus of Formula II. The Suzuki coupling reaction can be carried out as described in Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (9) of Reaction Scheme IX, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXXI is converted to a 1*H*-imidazo[4,5-*c*]quinolinyl compound of

Formula LXXII. Step (9) can be carried out as described for step (9) of Reaction Scheme III, and the product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IX



For certain embodiments, compounds of the invention can be prepared according to Reaction Scheme X, where R, R_2, R_4, Hal, and n are as defined above and X_{1-1} is selected from the group consisting of C_{1-10}alkylene, C_{4-10}alkenylene, and C_{4-10}alkynylene, wherein the terminal carbon atoms of alkenylene and alkynylene are tetrahedral. In step (1) a 3-nitroquinolin-4-amine of Formula LXXIII is reduced to provide a quinoline-3,4-diamine of Formula LXXIV. The reaction can be carried out as in step (7) of Reaction Scheme II. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods. Many 3-nitroquinolin-4-amines of Formula LXXIII are

known or can be prepared using known synthetic methods, see for example, U.S. Patent Nos. 4,689,338; 5,175,296; and 5,389,640; and the references cited therein.

In step (2) of Reaction Scheme X, a quinoline-3,4-diamine of Formula LXXIV is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXV. The reaction can be conveniently carried out as described in step (8) of Reaction Scheme II. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (3) of Reaction Scheme X, a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXV is reacted with sodium hydride to form an alkoxide, which is reacted with a vinyl sulfone to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXVI. The reaction can be carried out by adding catalytic sodium hydride dispersed in mineral oil to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXV and a vinyl sulfone of the formula CH_2=CH-S(O)$_2$-R_4 in a suitable solvent such DMF or tetrahydrofuran. The reaction can be run at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

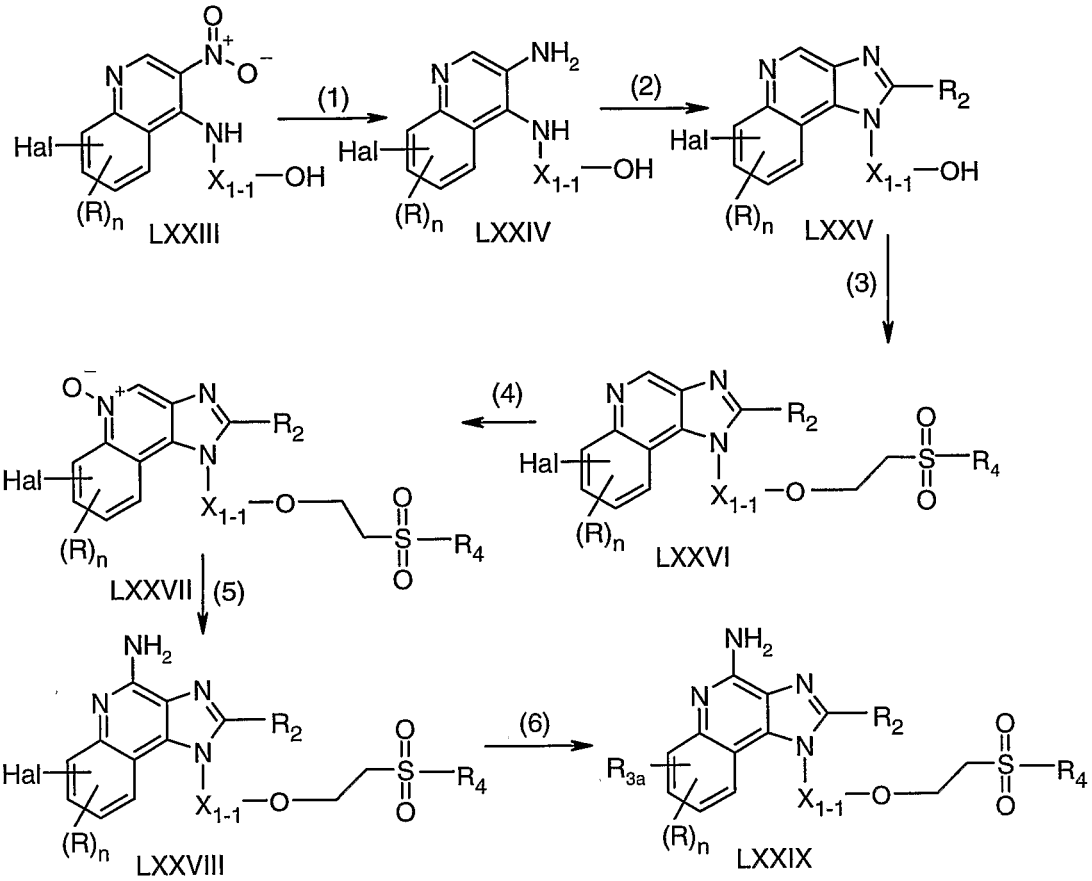
In step (4) of Reaction Scheme X, a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXVI is oxidized to provide an *N*-oxide of Formula LXXVII. The reaction can be conveniently carried out as in step (9) of Reaction Scheme II.

In step (5) an *N*-oxide of Formula LXXVII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula LXXVIII. The reaction is carried as in step (10) of Reaction Scheme II. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (6) of Reaction Scheme X, a halogen-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula LXXVIII undergoes a coupling reaction with a boronic acid of Formula X, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$. The Suzuki coupling reaction can be carried out as described in Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LXXIX, which is a subgenus of Formula II. The product or

pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme X



For other embodiments, compounds of the invention can be prepared according to Reaction Scheme XI, where R, R_2, R_4, R_8, X, Hal, and n are as defined above. In step (1) of Reaction Scheme XI, the hydroxy group of a 3-nitroquinolin-4-amine of Formula LXXX is chlorinated using conventional methods to provide a 3-nitroquinolin-4-amine of Formula LXXXI. Many 3-nitroquinolin-4-amines of Formula LXXIII are known or can be prepared using known synthetic methods; see for example, U.S. Patent Nos. 4,689,338; 5,175,296; and 5,389,640; and the references cited therein. The chlorination is conveniently carried out by adding thionyl chloride to a solution of the 3-nitroquinolin-4-amine of Formula LXXX in a suitable solvent such as

dichloromethane. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (2) of Reaction Scheme XI, a 3-nitroquinolin-4-amine of Formula LXXXI is reduced to provide a quinoline-3,4-diamine of Formula LXXXII. The reduction can be carried out with sodium dithionite as described in step (7) of Reaction Scheme II. The product can be isolated by conventional methods.

In step (3) of Reaction Scheme XI, a quinoline-3,4-diamine of Formula LXXXII is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXIII. The reaction can be conveniently carried out as described in step (8) of Reaction Scheme II; the product can be isolated by conventional methods.

In step (4) of Reaction Scheme XI, the chloro group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXIII is displaced with potassium thioacetate to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXIV. The reaction is conveniently carried out by adding potassium thioacetate to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXIII in a suitable solvent such as DMF. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme XI, the thioacetate group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXIV is hydrolyzed under basic conditions to provide a thiol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXV. The reaction is conveniently carried out by adding a solution of sodium methoxide in methanol to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXIV in methanol. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (6) of Reaction Scheme XI, the thiol group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXV is oxidized to a sulfonyl chloride of Formula LXXXVI. The reaction is conveniently carried out by adding a solution of sodium chlorate in a suitable solvent such as water to a solution of a thiol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXV in hydrochloric acid. The reaction can be carried out at a subambient temperature such as 0 °C, and the product can be isolated using conventional methods.

Alternatively, steps (4), (5), and (6) can be replaced with steps (4a) and (5a) of Reaction Scheme XI. In step (4a), the chloro group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXIII is displaced with thiourea to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXVII. The reaction is conveniently carried out by adding thiourea and a catalytic amount of potassium iodide to a solution of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXIII in a suitable solvent such as DMF. The reaction can be carried out at an elevated temperature, such as 110 °C, and the product can be isolated using conventional methods.

In step (5a) of Reaction Scheme XI, the thiourea group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXVII is converted to a sulfonyl chloride of Formula LXXXVI under the conditions described in step (6).

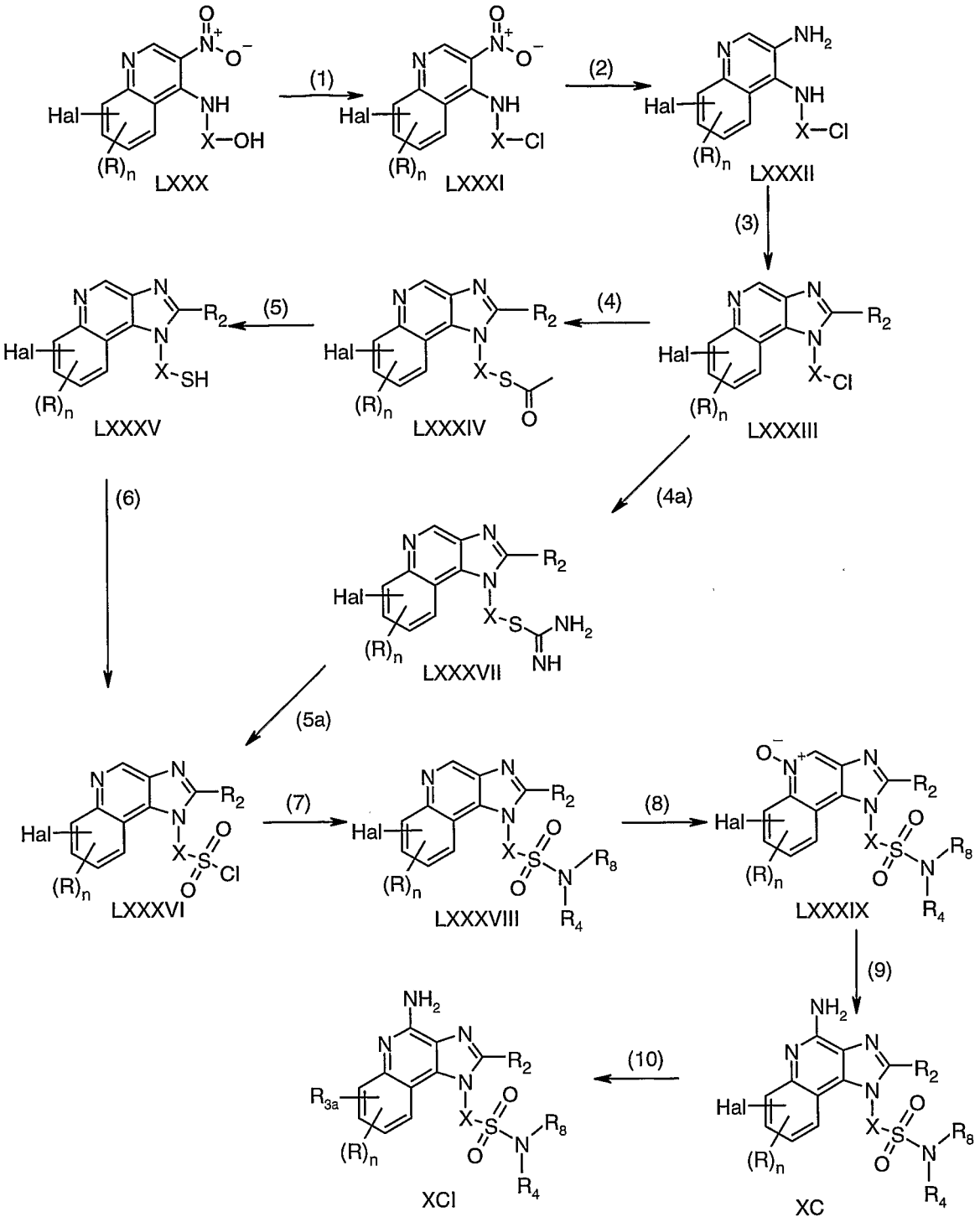
In step (7) of Reaction Scheme XI, the sulfonyl chloride of Formula LXXXVI is treated with an amine or an amine salt to provide a sulfonamide of Formula LXXXVIII. The reaction is conveniently carried out by adding an amine of Formula $NH(R_4)(R_8)$ to a sulfonyl chloride of Formula LXXXVI in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods. Alternatively, step (7) can be carried out by adding an amine hydrochloride of Formula $(R_4)(R_8)NH\bullet HCl$ followed by aqueous potassium carbonate to a solution of a sulfonyl chloride of Formula LXXXVI in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In steps (8) and (9) of Reaction Scheme XI, a sulfonamide-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula LXXXVIII is oxidized in step (8) to afford a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula LXXXIX, which is aminated in step (9) to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XC. Steps (8) and (9) of Reaction Scheme XI can be carried out as described in steps (9) and (10) of Reaction Scheme II.

In step (10) of Reaction Scheme XI, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XC is coupled with a boronic acid of Formula X, an anhydride thereof, or boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ to provide a 1*H*-

imidazo[4,5-*c*]quinolin-4-amine of Formula XCI, which is a subgenus of Formula II. Step (10) can be carried out as described in Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

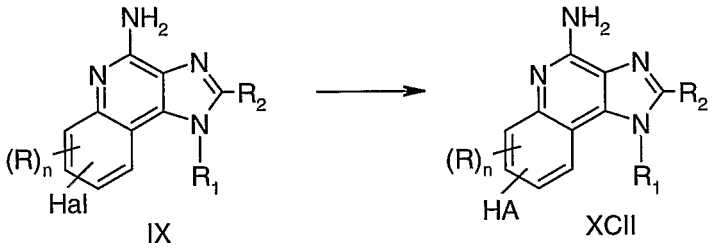
Reaction Scheme XI



For other embodiments, compounds of the invention can be prepared according to Reaction Scheme XII, wherein R, R_1, R_2, Hal, and n are as defined above, and HA is a heteroaryl group attached at a nitrogen atom. In Reaction

Scheme XII, a halogen-substituted imidazoquinolin-4-amine of Formula IX undergoes a copper-catalyzed amination with a nitrogen-containing heteroaryl compound to provide an imidazoquinolin-4-amine of Formula XCII, which is a subgenus of Formula II. Several nitrogen-containing heteroaryl compounds, such as imidazole and pyrazole, are commercially available; others can be prepared by known methods. The reaction is conveniently carried out by combining the imidazoquinolin-4-amine of Formula IX and the nitrogen-containing heteroaryl compound in the presence of copper (I) iodide, potassium phosphate, and *trans*-1,2-diaminocyclohexane in a suitable solvent such as 1,4-dioxane. The reaction can be carried out at an elevated temperature such as 110 °C. The compound or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme XII



Pharmaceutical Compositions and Biological Activity

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

The term "therapeutically effective amount" or "effective amount" means an amount of the compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, cytokine inhibition, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound 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, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about

50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg, of the compound to the subject. 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.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention 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 of the invention have been shown to modulate (e.g., induce or inhibit) the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that compounds of the invention are useful as immune response modifiers that can modulate 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 certain compounds according to the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by certain compounds 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 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 composition of the invention to the animal. The animal to which the compound or composition 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 may provide therapeutic treatment. Alternatively, the compound may be administered to the animal prior to the animal aquiring the disease so that administration of the compound may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, certain compounds of the invention 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. Certain compounds may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, certain compounds may cause proliferation and differentiation of B-lymphocytes.

Certain compounds of the invention also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of compounds of the invention.

Other cytokines whose production is inhibited by the administration of certain compounds according to the invention include tumor necrosis factor-α (TNF-α). Among other effects, inhibition of TNF-α production can provide prophylaxis or therapeutic treatment of diseases in animals in which TNF is mediated, making the compounds 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 composition of the invention to the animal. The animal to which the compound 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 may provide therapeutic treatment. Alternatively, the compound may be administered to the animal prior to the animal aquiring the disease so that administration of the compound 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 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 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 IRMs 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 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; and

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

(e) T_H2-mediated, atopic, and autoimmune diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, Ommen's syndrome, discoid lupus, alopecia areata, inhibition of keloid formation and other types of scarring, and enhancing would healing, including chronic wounds.

IRMs identified herein also 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; recombinant proteins; glycoproteins; peptides; 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.

IRMs may also be particularly helpful in individuals having compromised immune function. For example, IRM compounds 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, a neoplastic disease, may be treated in an animal in need there of (having the disease) by administering a therapeutically effective amount of a compound or salt of Formula I, II, III, IV, V, VI, VII, VIII, XLVI, or a combination thereof to the animal.

An amount of a compound 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. 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 composition 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 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 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, WO 03/080114, WO 03/045494, WO 02/024225, WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2002/0193729 and 2003/0139364.

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

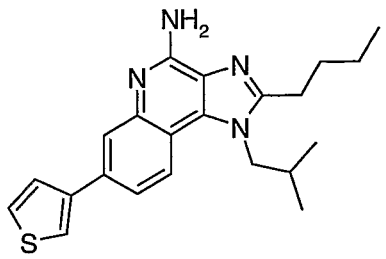
In the examples below some of the compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC-TOFMS and the appropriate fractions were combined and centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. In order to maximize purity, the compounds were sent through the purification process twice. Column: Phenomenex Luna C18(2), 21.2 x 50 millimeters (mm), 10 micron particle size, 100 Angstrom (Å) pore; flow rate: 25 milliliters per minutes (mL/min); non-linear gradient elution from 5-95% B in 9 min (first purification run) and from 5-65% B in 16 min (second purification run), then hold at 95% B for 2 min, where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroactic acid/acetonitrile; fraction collection by mass-selective triggering.

A variety of chromatographic conditions were used for the prep HPLC purification of other compounds shown in the examples below using either the Phenomenex Luna C18(2) column (21.2 x 50 millimeters (mm), 10 micron particle size) or a Waters Xterra C18 column (19 x 50 mm, 5 micron particle size). Elution was carried out in a non-linear gradient from 95:5 to 5:95 A:B, where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroactic acid/acetonitrile; fraction collection was performed by mass-selective triggering.

Some of the compounds prepared by Suzuki coupling were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) prior to prep HPLC purification. The following procedure was used. The product from the coupling reaction was dissolved in 1N hydrochloric acid (3 mL) to adjust to pH 5-7 and 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 1% ammonia in methanol (2 x 5 mL) was then passed through the cartridge optionally using light nitrogen pressure, and the basic solution was collected and concentrated.

Example 1

2-Butyl-1-isobutyl-7-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A mixture of triethyl orthoformate (154 grams (g), 1.04 moles (mol) and Meldrum's acid (142 g, 0.983 mol) was heated to 55°C for 4 hours (h). After cooling to 50°C, a solution of 3-bromoaniline (162.6 g, 0.945 mol) in ethanol (300 mL) was added such that the temperature of the reaction was maintained between 50-55°C. After half of the 3-bromoaniline had been added, stirring became difficult due to the formation of solids, so more ethanol (1 liter (L)) was added to facilitate stirring. Upon complete addition, the reaction was cooled to room temperature (RT), and the solids were collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless, and the product was dried at 65°C under vacuum to afford 287 g of 5-[(3-bromophenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.19 (brd, J = 12.8 Hz, 1H), 8.60 (d, J = 14.0 Hz, 1H), 7.44-7.38 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.18 (ddd, J = 8.0, 2.2, 0.9 Hz, 1H), 1.75 (s, 6H).

Part B

7-Bromoquinolin-4-ol was prepared in accordance with the literature procedure (D. Dibyendu et al., *J. Med. Chem.*, *41*, 4918-4926 (1998)) or by thermolysis of 5-[(3-bromophenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione in DOWTHERM A heat transfer fluid and had the following spectral properties:

^{1}H NMR (300 MHz, d_6-DMSO) δ 11.70 (brs, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.44 (dd, J = 8.7, 1.9 Hz, 1H), 6.05 (d, J = 7.5 Hz, 1H).

Part C

A stirred suspension of 7-bromoquinolin-4-ol (162 g, 0.723 mol) in propionic acid (1500 mL) was brought to 110°C. 70% Nitric acid (85 g) was added dropwise over 1 h such that the temperature was maintained between 110-115°C. After half of the nitric acid had been added, stirring became difficult due to the formation of solids and an additional 200 mL of propionic acid was added. Upon complete addition, the reaction was stirred for 1 h at 110°C, cooled to room temperature, and the solid was collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless (800 mL), and the product was dried at 60°C under vacuum to afford 152 g of 7-bromo-3-nitro-quinolin-4-ol as a pale yellow solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 13.0 (brs, 1H), 9.22 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.66 (dd, J = 8.7, 1.9 Hz, 1H).

Part D

7-Bromo-3-nitroquinolin-4-ol (42 g, 156 millimoles (mmol)) was suspended in $POCl_3$ (130 mL) and brought to 102°C under an atmosphere of N_2. After 45 min, all of the solids had dissolved, so the reaction was cooled to room temperature (RT). The resulting solids were collected by filtration, washed with H_2O, and then partitioned with CH_2Cl_2 (3 L) and 2M Na_2CO_3 (500 mL). The organic layer was separated, washed with H_2O (1x), dried over Na_2SO_4, filtered, and concentrated to afford 33.7 g of 7-bromo-4-chloro-3-nitroquinoline as a beige solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 7.90 (dd, J = 8.9, 2.1 Hz, 1H).

Part E

7-Bromo-4-chloro-3-nitroquinoline (33.5 g, 117 mmol) and Et_3N (13.0 g, 128 mmol) were dissolved in CH_2Cl_2 (500 mL) and cooled on an ice bath. Isobutylamine (9.36 g, 128 mmol) was added in one portion and then the

reaction was allowed to warm to room temperature. After 2 h, the reaction mixture was washed with water (500 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 38.0 g of a yellow solid. Recrystallization from refluxing isopropanol (1.1 L) afforded 34.0 g of (7-bromo-3-nitroquinolin-4-yl)isobutylamine as yellow needles.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (brs, 1H), 9.35 (s, 1H), 8.16 (d, J = 9.1 Hz, 1H), 8.16 (d, J = 2.2 Hz, 1H), 7.57 (dd, J = 9.1, 2.2 Hz, 1H), 3.75 (dd, J = 6.6, 5.0 Hz, 2H), 2.14-2.01 (m, 1H), 1.10 (d, J = 6.9 Hz, 6H).

Part F

A solution of $Na_2S_2O_4$ (193 g) in H_2O (1 L) was added to a boiling solution of (7-bromo-3-nitroquinolin-4-yl)isobutylamine (32.0 g, 99 mmol) in isopropanol (1 L). Upon complete addition, the reaction mixture was cooled to room temperature and the bulk of the isopropanol was removed on a rotary evaporator. The resulting mixture was extracted with CH_2Cl_2 (3x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 39.5 g of the crude 7-bromo-N^4-isobutylquinoline-3,4-diamine as a yellow solid.

Part G

7-Bromo-N^4-isobutylquinoline-3,4-diamine (39.4 g of crude material), trimethyl orthovalerate (32 g, 0.20 mol), and pyridine hydrochloride (0.31 g, 2.7 mmol) were combined with anhydrous toluene (500 mL) and heated to reflux for 30 min. The reaction was cooled to room temperature, concentrated, and the residue was purified by chromatography on silica gel (75% ethyl acetate in hexane to 100% ethyl acetate gradient) to afford 21.2 g of 7-bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.43 (d, J = 2.2 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.70 (dd, J = 9.1, 2.2 Hz, 1H), 4.29 (d, J = 7.5 Hz, 2H), 2.97-2.91 (m, 2H), 2.40-2.26 (m, 1H), 2.01-1.90 (m, 2H), 1.52 (sextet, J = 7.5 Hz, 2H), 1.02 (d, J = 6.9 Hz, 6H), 1.01 (t, J = 7.3 Hz, 3H);

MS *m/z* ($M+1^+$) calcd 362.1, obsd 362.1.

Part H

To a solution of 7-bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline (10.8 g, 30.0 mmol) in CH_2Cl_2 (300 mL) was added 3-chloroperoxybenzoic acid (10.4 g of approximately 77% purity). The reaction was allowed to stir overnight and was washed with 2M Na_2CO_3 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford 13.6 g orange solid. Recrystallization from boiling ethyl acetate (300 mL) afforded 8.25 g of 7-bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline 5-oxide as a yellow powder.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, *J* = 1.9 Hz, 1H), 9.00 (s, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.81 (dd, *J* = 9.1, 2.2 Hz, 1H), 4.26 (d, *J* = 7.5 Hz, 2H), 2.94-2.89 (m, 2H), 2.37-2.23 (m, 1H), 1.97-1.87 (m, 2H), 1.51 (sextet, *J* = 7.4 Hz, 2H), 1.03 (d, *J* = 6.6 Hz, 6H), 1.01 (t, *J* = 7.3 Hz, 3H);

MS *m/z* ($M+1^+$) calcd 378.1, obsd 378.1.

Part I

To a vigorously stirred mixture of 7-bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline 5-oxide (345 mg, 0.92 mmol) in CH_2Cl_2 (7 mL) and NH_4OH (0.50 mL of 30%) was added *p*-toluenesulfonyl chloride (175 mg, 0.92 mmol) in one portion. After 15 h, the reaction mixture was diluted with CH_2Cl_2 and washed with 2 M Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (2x), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford 331 mg of a yellow solid. Recrystallization from boiling isopropanol (3 mL) followed by purification on silica gel (40% acetone in toluene to 50% acetone in toluene gradient) afforded 208 mg of 7-bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. 198-200°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.2 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.40 (dd, *J* = 8.7, 1.9 Hz, 1H), 5.44 (s, 2H), 4.22 (d, *J* = 7.8 Hz, 2H), 2.92-2.86 (m, 2H), 2.38-2.24 (m, 1H), 1.93-1.83 (m, 2H), 1.50 (sextet, *J* = 7.5 Hz, 2H), 1.00 (d, *J* = 6.9 Hz, 6H), 1.00 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 152.0, 146.2, 133.3, 129.9, 127.2, 125.2, 121.1, 120.5, 114.6, 52.8, 30.3, 29.4, 27.7, 22.8, 20.0, 14.1;

MS *m/z* ($M+1^+$) calcd 375.1, obsd 375.2;

Anal. Calcd for $C_{18}H_{23}BrN_4$: C, 57.60; H, 6.18; N, 14.93. Found: C, 57.54; H, 6.17; N, 14.98.

Part J

7-Bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (751 mg, 2.00 mmol), thiophene-3-boronic acid (269 mg, 2.10 mmol), and *n*-propanol (3.6 mL) were combined in a reaction vessel and placed under an atmosphere of N_2. $Pd(OAc)_2$ (1.3 mg, 0.0060 mmol), triphenylphosphine (4.7 mg, 0.018 mmol), Na_2CO_3 (1.2 mL of a 2 M solution, 2.4 mmol), and H_2O (0.7 mL) were added, and the reaction mixture was heated to reflux in an oil bath for 2.5 h. Upon cooling to RT, the solid product was collected by filtration and washed with H_2O and ethanol. Purification on silica gel (5%-6% methanol (MeOH) in CH_2Cl_2 gradient) afforded 700 mg of product which was recrystallized from boiling isopropanol (20 mL) to yield 535 mg of 2-butyl-1-isobutyl-7-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white powder, m.p. 229-230°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 1.9 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.61-7.58 (m, 2H), 7.55 (dd, J = 5.2, 1.4 Hz, 1H), 7.42 (dd, J = 5.2, 3.0 Hz, 1H), 5.39 (s, 2H), 4.26 (d, J = 7.5 Hz, 2H), 2.93-2.88 (m, 2H), 2.46-2.32 (m, 1H), 1.94-1.84 (m, 2H), 1.51 (sextet, J = 7.4 Hz, 2H), 1.03 (d, J = 6.6 Hz, 6H), 1.01 (t, J = 7.5 Hz, 3H);

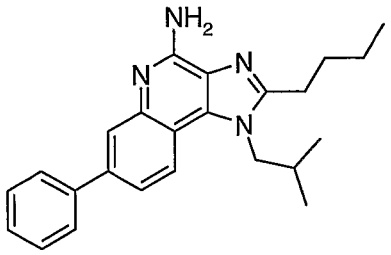
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 151.7, 145.5, 142.3, 134.3, 133.6, 127.2, 126.53, 126.47, 124.6, 121.0, 120.6, 120.4, 114.8, 52.8, 30.4, 29.5, 27.8, 22.9, 20.0, 14.1;

MS *m/z* ($M+1^+$) calcd 379.1956, obsd 379.1943;

Anal. Calcd for $C_{22}H_{26}N_4S$: C, 69.80; H, 6.92; N, 14.80; S, 8.47. Found: C, 69.45; H, 7.10; N, 14.90; S, 8.44.

Example 2

2-Butyl-1-isobutyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



7-Bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and benzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. Purification by chromatography on silica gel (20% acetone in toluene to 60% acetone in toluene gradient) afforded 2-butyl-1-isobutyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. >250°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 1.9 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.77-7.74 (m, 2H), 7.61 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.50-7.45 (m, 2H), 7.36 (tt, *J* = 7.3, 1.5 Hz, 1H), 5.40 (s, 2H), 4.28 (d, *J* = 7.5 Hz, 2H), 2.94-2.89 (m, 2H), 2.48-2.34 (m, 1H), 1.95-1.84 (m, 2H), 1.52 (sextet, *J* = 7.4 Hz, 2H), 1.04 (d, *J* = 6.6 Hz, 6H), 1.01 (t, *J* = 7.3 Hz, 3H);

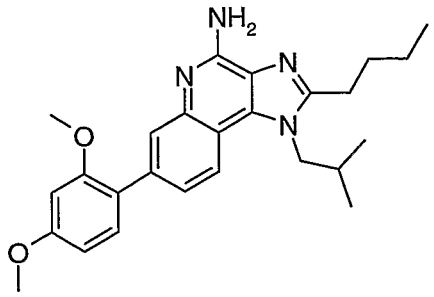
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 151.7, 145.3, 141.0, 139.6, 133.6, 129.1, 127.6, 127.4, 127.2, 125.4, 121.6, 120.4, 114.9, 52.9, 30.4, 29.5, 27.8, 22.9, 20.0, 14.1;

MS *m/z* ($M+1^+$) calcd 373.2, obsd 373.2;

Anal. Calcd for $C_{24}H_{28}N_4$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.16; H, 7.62; N, 14.95.

Example 3

2-Butyl-7-(2,4-dimethoxyphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



7-Bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline and 2,4-dimethoxybenzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. The resulting 2-butyl-7-(2,4-dimethoxyphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline was oxidized and then aminated according to the general procedures described in Parts H and I of Example 1 and purified by chromatography on silica gel (8% methanol in CH_2Cl_2 to 10% methanol in CH_2Cl_2 gradient) followed by recrystallization from 1/1 ethyl acetate/hexane to afford 2-butyl-7-(2,4-dimethoxyphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a pale orange solid, m.p. 187-189°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.6 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.53 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.40-7.37 (m, 1H), 6.62-6.58 (m, 2H), 5.38 (s, 2H), 4.25 (d, *J* = 7.5 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.93-2.88 (m, 2H), 2.50-2.36 (m, 1H), 1.94-1.84 (m, 2H), 1.51 (sextet, *J* = 7.4 Hz, 2H), 1.02 (d, *J* = 6.6 Hz, 6H), 1.01 (t, *J* = 7.2 Hz, 3H);

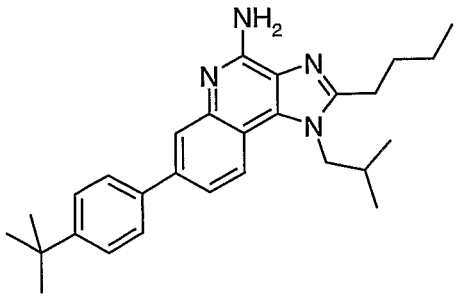
^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 157.8, 152.9, 151.4, 145.0, 137.2, 133.6, 131.7, 127.7, 127.1, 124.3, 123.5, 119.3, 114.3, 105.0, 99.3, 55.8, 55.6, 52.8, 30.3, 29.4, 27.7, 22.9, 20.0, 14.1;

MS *m/z* ($M+1^+$) calcd 433.2604, obsd 433.2600;

Anal. Calcd for $C_{26}H_{32}N_4O_2 \cdot 0.17H_2O$: C, 71.67; H, 7.48; N, 12.86. Found: C, 71.25; H, 7.46; N, 12.81. Water content determined by Karl-Fischer analysis.

Example 4

2-Butyl-7-(4-*tert*-butylphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



7-Bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and 4-*tert*-butylbenzeneboronic were coupled according to the general procedure described in Part J of Example 1. Purification by chromatography on silica gel (5% methanol in CH_2Cl_2 to 6% methanol in CH_2Cl_2 gradient) followed by recrystallization from ethyl acetate afforded 2-butyl-7-(4-*tert*-butylphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. 219-220°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 1.9 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.71 (dm, J = 8.4 Hz, 2H), 7.60 (dd, J = 8.6, 2.1 Hz, 1H), 7.51 (dm, J = 8.7 Hz, 2H), 5.38 (s, 2H), 4.27 (d, J = 7.5 Hz, 2H), 2.94-2.89 (m, 2H), 2.48-2.35 (m, 1H), 1.92-1.84 (m, 2H), 1.51 (sextet, J = 7.4 Hz, 2H), 1.38 (s, 9H), 1.03 (d, J = 6.6 Hz, 6H), 1.01 (t, J = 7.3 Hz, 3H);

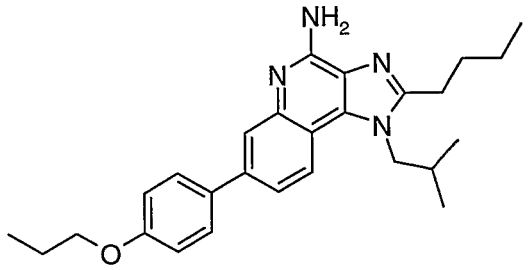
^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 151.6, 150.6, 145.4, 139.4, 138.0, 133.6, 127.1, 127.0, 126.0, 125.1, 121.5, 120.3, 114.8, 52.8, 34.8, 31.6, 30.4, 29.4, 27.8, 22.9, 20.0, 14.1;

MS *m/z* ($M+1^+$) calcd 429.3, obsd 429.5;

Anal. Calcd for $C_{28}H_{36}N_4$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.10; H, 8.45; N, 13.02.

Example 5

2-Butyl-1-isobutyl-7-(4-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



7-Bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and 4-propoxybenzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. The product was recrystallized from isopropanol, collected by filtration, dissolved in CH_2Cl_2, and then precipitated with hexanes to afford 2-butyl-1-isobutyl-7-(4-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a pale yellow solid, m.p. 194-197°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 1.9 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.69 (dm, *J* = 8.7 Hz, 2H), 7.55 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.01 (dm, *J* = 9.0 Hz, 2H), 5.42 (s, 2H), 4.25 (d, *J* = 7.5 Hz, 2H), 3.98 (t, *J* = 6.7 Hz, 2H), 2.93-2.88 (m, 2H), 2.40 (septet, *J* = 6.9 Hz, 1H), 1.94-1.79 (m, 4H), 1.51 (sextet, *J* = 7.4 Hz, 2H), 1.06 (t, *J* = 7.5 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 6H), 1.01 (t, *J* = 7.5 Hz, 3H);

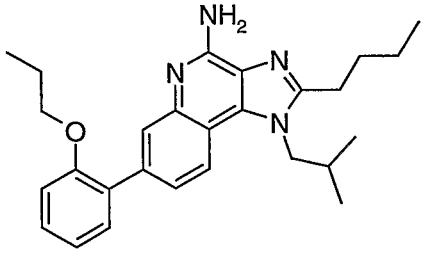
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 154.0, 151.6, 145.5, 139.3, 133.6, 133.3, 128.3, 127.1, 124.8, 121.2, 120.3, 115.1, 114.5, 69.8, 52.8, 30.4, 29.4, 27.7, 22.87, 22.84, 20.0, 14.1, 10.8;

MS *m/z* ($M+1^+$) calcd 431.2811, obsd 431.2821;

Anal. Calcd for $C_{27}H_{34}N_4O$: C, 75.31; H, 7.96; N, 13.01. Found: C, 75.20; H, 8.18; N, 12.96.

Example 6

2-Butyl-1-isobutyl-7-(2-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



7-Bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and 2-propoxybenzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. The product was recrystallized from isopropanol, collected by filtration, dissolved in CH_2Cl_2, and then precipitated with hexanes to afford 2-butyl-1-isobutyl-7-(2-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, m.p. 174.5-176.0°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.9 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.61 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.34-7.29 (m, 1H), 7.07-7.00 (m, 2H), 5.46 (s, 2H), 4.27 (d, *J* = 7.5 Hz, 2H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.94-2.88 (m, 2H), 2.41 (septet, *J* = 6.8 Hz, 1H), 1.94-1.84 (m, 2H), 1.76 (sextet, *J* = 7.1 Hz, 2H), 1.51 (sextet, *J* = 7.4 Hz, 2H), 1.03-0.93 (m, 12H);

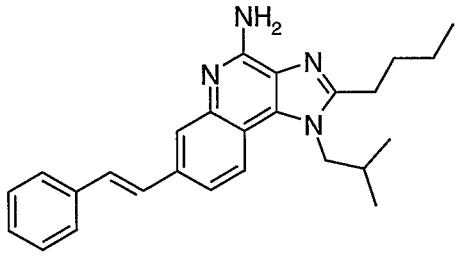
^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 153.9, 151.4, 145.1, 137.6, 133.6, 131.3, 131.0, 128.8, 127.9, 127.2, 124.5, 121.1, 118.9, 114.5, 113.0, 70.4, 52.8, 30.4, 29.4, 27.8, 22.9, 22.8, 20.0, 14.1, 10.9;

MS *m/z* ($M+1^+$) calcd 431.2811, obsd 431.2809;

Anal. Calcd for $C_{27}H_{34}N_4O \cdot 0.16H_2O$: C, 74.82; H, 7.98; N, 12.93. Found: C, 74.64; H, 7.99; N, 12.78. Water content determined by Karl-Fischer titration.

Example 7

2-Butyl-1-isobutyl-7-[(E)-2-phenylethenyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



7-Bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and *trans*-2-phenylvinylboronic acid were coupled according to the general procedure described in Part J of Example 1. Recrystallization from toluene followed by chromatography on silica gel (8% methanol in CH_2Cl_2) afforded 2-butyl-1-isobutyl-7-[(E)-2-phenylethenyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine, m.p. 215-216°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.6 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.57-7.52 (m, 3H), 7.40-7.35 (m, 2H), 7.30-7.24 (m, 3H), 5.44 (s, 2H), 4.24 (d, *J* = 7.5 Hz, 2H), 2.93-2.87 (m, 2H), 2.37 (septet, *J* = 6.9 Hz, 1H), 1.94-1.83 (m, 2H), 1.51 (sextet, *J* = 7.4 Hz, 2H), 1.02 (d, *J* = 7.2 Hz, 6H), 1.00 (t, *J* = 7.5 Hz, 3H);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (center of AB pattern, *J* = 16.4 Hz);

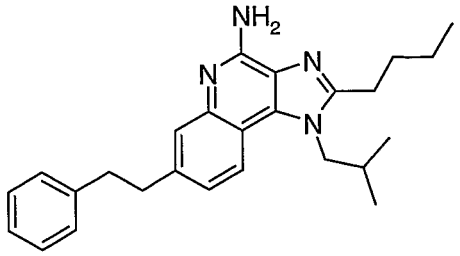
^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 151.6, 145.1, 137.6, 136.0, 133.6, 129.2, 128.9, 128.8, 127.9, 127.1, 126.8, 125.6, 120.5, 120.2, 115.1, 52.8, 30.4, 29.4, 27.7, 22.9, 20.0, 14.1;

MS *m/z* ($M+1^+$) calcd 399.3, obsd 399.2;

Anal. Calcd for $C_{26}H_{30}N_4$: C, 78.36; H, 7.59; N, 14.06. Found: C, 78.05; H, 7.61; N, 14.01.

Example 8

2-Butyl-1-isobutyl-7-phenethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



2-Butyl-1-isobutyl-7-[(E)-2-phenylethenyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine (562 mg, 1.41 mmol) was hydrogenated in a Parr bottle over palladium on carbon (10%) until the starting material was consumed as judged by high performance liquid chromatography (HPLC) and thin layer chromatography (TLC) analyses. Purification on silica (5% to 10% methanol in CH_2Cl_2 gradient) followed by recrystallization from boiling CH_3CN afforded 150 mg of 2-butyl-1-isobutyl-7-phenethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine, m.p. 181-182°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.32-7.14 (m, 6H), 5.44 (s, 2H), 4.23 (d, *J* = 7.5 Hz, 2H), 3.11-3.00 (m, 4H), 2.92-2.87 (m, 2H), 2.43-2.30 (m, 1H), 1.93-1.83 (m, 2H), 1.50 (sextet, *J* = 7.4 Hz, 2H), 1.00 (d, *J* = 6.6 Hz, 6H), 1.00 (t, *J* = 7.3 Hz, 3H);

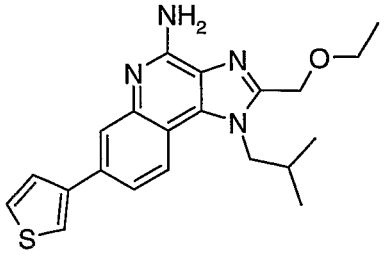
^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 151.4, 145.1, 142.1, 140.8, 133.7, 128.7, 128.6, 126.8, 126.5, 126.1, 123.4, 119.8, 114.0, 52.8, 38.1, 38.0, 30.4, 29.4, 27.7, 22.9, 20.0, 14.1;

MS *m/z* ($M+1^+$) calcd 401.2705, obsd 401.2705;

Anal. Calcd for $C_{26}H_{32}N_4$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.95; H, 8.02; N, 14.04.

Example 9

2-Ethoxymethyl-1-isobutyl-7-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of 7-bromo-N^4-isobutylquinoline-3,4-diamine (85 g, prepared according to Part F of Example 1) in anhydrous pyridine (413 mL) was immersed in an ice bath, and ethoxyacetyl chloride (36.9 g, 300 mmol) was added. The reaction was allowed to warm to room temperature and was then heated in an oil bath held at 85°C for 3.5 h. The reaction mixture was concentrated under vacuum, and the residue was taken up in diethyl ether and washed with 2M Na_2CO_3 (2x) followed by H_2O (1x). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Recrystallization of the resulting solid from boiling 15% ethyl acetate in hexanes afforded 43.0 g of 7-bromo-2-ethoxymethyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline as brown crystals.
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.45 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 9.1 Hz, 1H), 7.74 (dd, J = 8.7, 2.2 Hz, 1H), 4.88 (s, 2H), 4.49 (d, J = 7.5 Hz, 2H), 3.61 (q, J = 7.1 Hz, 2H), 2.45-2.31 (m, 1H), 1.24 (t, J = 7.0 Hz, 3H), 1.01 (d, J = 6.6 Hz, 6H);
MS *m/z* ($M+1^+$) calcd 364.1, obsd 364.1.

Part B

7-Bromo-2-ethoxymethyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline was oxidized and then aminated according to the general procedures described in Parts H and I of Example 1. Purification by recrystallization from isopropanol afforded 7-bromo-2-ethoxymethyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as yellow needles.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 2.2 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.39 (dd, J = 8.7, 2.2 Hz, 1H), 5.80 (s, 2H), 4.80 (s, 2H), 4.38 (d, J = 7.5 Hz, 2H), 3.60 (q, J = 7.1 Hz, 2H), 2.42-2.28 (m, 1H), 1.24 (t, J = 6.9 Hz, 3H), 0.99 (d, J = 6.6 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 149.9, 146.5, 134.1, 129.8, 127.1, 125.3, 121.5, 121.1, 114.5, 66.5, 65.5, 53.1, 29.2, 20.0, 15.2;

Anal. Calcd for $C_{17}H_{21}BrN_4O$: C, 54.12; H, 5.61; N, 14.85. Found: C, 54.16; H, 5.61; N, 14.67.

Part C

7-Bromo-2-ethoxymethyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and thiophene-3-boronic acid were coupled according to the general procedure described in Part J of Example 1. Recrystallization from isopropanol followed by purification on silica gel (5% methanol in CH_2Cl_2 to 7% methanol in CH_2Cl_2 gradient) afforded 2-ethoxymethyl-1-isobutyl-7-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a pale yellow solid, m.p. 187-189°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 1.9 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.63-7.60 (m, 2H), 7.55 (dd, J = 5.2, 1.4 Hz, 1H), 7.43 (dd, J = 5.2, 3.0 Hz, 1H), 5.44 (s, 2H), 4.83 (s, 2H), 4.45 (d, J = 7.5 Hz, 2H), 3.61 (q, J = 7.1 Hz, 2H), 2.44 (septet, J = 6.8 Hz, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.04 (d, J = 6.9 Hz, 6H);

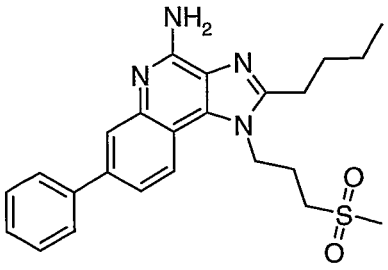
^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 149.7, 145.8, 142.2, 134.9, 134.5, 127.1, 126.5, 124.6, 121.1, 120.84, 120.82, 114.8, 66.5, 65.6, 53.1, 29.3, 20.1, 15.3;

MS *m/z* ($M+1^+$) calcd 381.1749, obsd 381.1763;

Anal. Calcd for $C_{21}H_{24}N_4OS$: C, 66.29; H, 6.36; N, 14.72. Found: C, 66.54; H, 6.37; N, 14.73.

Example 10

2-Butyl-1-(3-methanesulfonylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of 3-bromoaniline (344 g, 2.00 mol) and phenyl boronic acid (268 g, 2.2 mol) in *n*-propanol (3.5 L) was sparged with N_2 for 10 min. To this solution was added $Pd(OAc)_2$ (1.35 g, 6.0 mmol), triphenylphosphine (4.72 g, 18.0 mmol), Na_2CO_3 (1.2 L of a 2 M solution, 2.4 mol), and H_2O (700 mL). The reaction was brought to reflux under a N_2 atmosphere over a period of 45 min and then cooled to RT and transferred to a separatory funnel. The clear aqueous layer was drawn off (1.1 L), and the organic layer was washed with brine (3x500 mL). The organic layer was treated with charcoal (90 g of Darco G-60) and $MgSO_4$ (160 g) and was filtered through CELITE filter agent, washing with ethyl acetate. The filtrate was concentrated (420 g of an orange oil), dissolved in 1.1 L of 1/1 hexane/isopropanol, filtered to remove insoluble solid and then diluted with an additional 1.9 L of 1/1 hexane/isopropanol. The resulting solution was cooled in an ice bath and then anhydrous HCl in ether (1.05 L of a 2 M solution, 2.1 mol) was added. The solid was collected by filtration, washed with 700 mL diethyl ether (Et_2O), and dried at RT in a vacuum oven to obtain 345 g of the HCl salt of biphenyl-3-ylamine as yellow crystals. The free base was obtained by shaking the solid with *tert*-butyl methyl ether and 1 N NaOH followed by isolation in the usual fashion.

^1H NMR (300 MHz, $CDCl_3$): consistent with literature data (C.N. Carrigan et al., *J. Med. Chem.*, *45*, 2260-2276 (2002)).

Part B

Triethyl orthoformate (148 g, 1.00 mol), Meldrum's acid (137 g, 0.95 mol), and biphenyl-3-ylamine (155 g, 0.916 mol) were combined and treated

according to the general procedure described in Part A of Example 1 to obtain 283 g of 5-(biphenyl-3-ylaminomethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.33 (brd, J = 14.0 Hz, 1H), 8.72 (d, J = 15.0 Hz, 1H), 7.60-7.56 (m, 2H), 7.51-7.37 (m, 6H), 7.25-7.21 (m, 1H), 1.77 (s, 6H).

Part C

5-(Biphenyl-3-ylaminomethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (160.2 g, 496 mmol) was dissolved in 800 mL of DOWTHERM A heat transfer fluid at 100°C and added over 40 min by way of a cannula line to 1.3 L of preheated DOWTHERM A heat transfer fluid to 215°C. After complete addition, the reaction was held at 215°C for 90 min and then cooled to RT. The resulting solid was collected by filtration, sequentially washed with diethyl ether (1.7 L) and acetone (500 mL), and then dried in a vacuum oven at 70°C overnight. The resulting product (74.5 g) contained approximately 5% of the undesired isomer. This product was combined with material from a separate run (51.4 g) and slurried in 440 mL of refluxing ethanol. Filtration of the slurry while hot followed by sequential ethanol and diethyl ether rinses afforded 106.1 g of 7-phenylquinolin-4-ol as a tan solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 11.77 (brs, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.95-7.91 (m, 1H), 7.75-7.70 (m, 3H), 7.61 (dd, J = 8.4, 1.6 Hz, 1H), 7.56-7.50 (m, 2H), 7.47-7.42 (m, 1H), 6.05 (d, J = 7.5 Hz, 1H).

Part D

A stirred suspension of 7-phenylquinolin-4-ol (84.9 g, 384 mmol) in propionic acid (850 mL) was heated to 129°C. Nitric acid (70%, 45.0g) was added dropwise over 25 min, during which the temperature dropped to 124°C. The reaction was stirred an additional 3 h at that temperature and then cooled to 5°C on an ice bath. The resulting solid was collected by filtration, washed with ice cold ethanol (until washings were nearly colorless) and dried at 70°C in a vacuum oven overnight to obtain 83.2 g of 3-nitro-7-phenylquinolin-4-ol as a beige powder.

^{1}H NMR (300 MHz, d_6-DMSO) δ 13.00 (brs, 1H), 9.23 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 1.3 Hz, 1H), 7.83 (dd, J = 8.4, 1.9 Hz, 1H), 7.77-7.74 (m, 2H), 7.59-7.53 (m, 2H), 7.51-7.45 (m, 1H);
MS *m/z* ($M+1^+$) calcd 267.1, obsd 267.1.

Part E

A solution of phosphorous oxychloride (3.1 g, 20 mmol) in anhydrous *N,N*-dimethylformamide (DMF, 14 mL) was added to a suspension of 3-nitro-7-phenylquinolin-4-ol (5.0 g, 18.8 mmol) in 80 mL of DMF over 3 min. The reaction was allowed to stir for 1.5 h and then poured into 250 mL crushed ice. The resulting precipitate was collected by filtration, washed with H_2O, and dried under vacuum for 2 h. The crude 4-chloro-3-nitro-7-phenylquinoline thus obtained was used without further purification.

Part F

4-Chloro-3-nitro-7-phenylquinoline (5.3 g, 18.8 mmol) and 3-methylsulfanyl-propylamine (2.17 g, 20.6 mmol) were combined and treated according to the general procedure described in Part E of Example 1. Recrystallization from isopropanol afforded 6.2 g of (3-methylsulfanylpropyl)-(3-nitro-7-phenylquinolin-4-yl)amine as gold plates.

Part G

(3-Methylsulfanylpropyl)-(3-nitro-7-phenylquinolin-4-yl)amine (3.0 g, 8.5 mmol) was hydrogenated in a Parr bottle over Pt/C (0.3 g of 5%) in 42 mL of toluene for 1 h. The reaction mixture was filtered through CELITE filter agent, washed with methanol (100 mL) and $CHCl_3$ (50 mL), and then concentrated to afford 2.75 g of N^4-(3-methylsulfanylpropyl)-7-phenylquinoline-3,4-diamine as a brown oil.

Part H

N^4-(3-Methylsulfanylpropyl)-7-phenylquinoline-3,4-diamine (2.75 g, 8.49 mmol), trimethyl orthovalerate (1.7 g, 10 mmol), and pyridine hydrochloride (0.3 g) were dissolved in toluene (28 mL) and heated to reflux for

1.5 h, collecting the volatiles in a Dean-Stark trap. Upon cooling to room temperature, the solvent was removed under vacuum. The resulting solid was slurried in hexanes (100 mL) for 1 h and then collected by filtration to afford 3.0 g of 2-butyl-1-(3-methylsulfanylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinoline.

Part I

To a solution of 2-butyl-1-(3-methylsulfanylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinoline (3.0 g, 7.70 mmol) in $CHCl_3$ (39 mL) was added 3-chloroperoxybenzoic acid (6.74 g of approximately 77% purity) over 20 min. Aqueous NH_4OH (39 mL, 30%) was added, and to the resulting rapidly stirred biphasic suspension was added *p*-toluenesulfonyl chloride (1.8 g, 9.44 mmol) in one portion. After monitoring by thin layer chromatography indicated that no starting material remained, the reaction mixture was sequentially washed with 1% Na_2CO_3 (2x50 mL) and brine (50 mL); then dried (Na_2SO_4); filtered; and concentrated to a brown solid. Purification on silica (5% methanol in CH_2Cl_2) followed by recrystallization from CH_3CN afforded 0.50 g of 2-butyl-1-(3-methanesulfonylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as colorless needles, m.p. 214-216°C.

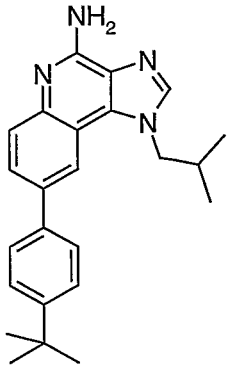
^{1}H NMR (300 MHz, d_6-DMSO) δ 8.21 (d, *J* =8.7 Hz, 1H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.78-7.75 (m, 2H), 7.57-7.48 (m, 3H), 7.41-7.36 (m, 1H), 6.52 (s, 2H), 4.69 (t, *J* = 7.5 Hz, 2H), 3.41 (t, *J* = 7.6 Hz, 2H), 3.02 (s, 3H), 2.95 (t, *J* = 7.8 Hz, 2H), 2.30-2.20 (m, 2H), 1.82 (pentet, *J* = 7.6 Hz, 2H), 1.47 (sextet, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H);

MS *m/z* ($M+1^+$) calcd 437.2, obsd 437.3;

Anal. Calcd for $C_{24}H_{28}N_4O_2S$: C, 66.03; H, 6.46; N, 12.86. Found: C, 66.09; H, 6.43; N, 12.57.

Example 11

8-(4-*tert*-Butylphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

To a solution of 1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (10.0 g, 41.6 mmol) in acetic acid (150 mL) was added Br_2 (10.0 g, 62.6 mmol), and after 24 h, the resulting solid was collected by filtration and washed with H_2O. The orange solid was suspended in a saturated aqueous solution of $NaHSO_3$, after which it was again collected and stirred with a 2 M solution of Na_2CO_3 for 18 h. The solid was collected by filtration, washed with H_2O, and azeotropically dried with toluene on a rotary evaporator. Purification on silica gel (7%-10% methanol in CH_2Cl_2 gradient) afforded 3.4 g of 8-bromo-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 2.2 Hz, 1H), 7.79 (s, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.59 (dd, J = 8.8, 2.2 Hz, 1H), 5.60 (s, 2H), 4.26 (d, J = 7.4 Hz, 2H), 2.37-2.27 (m, 1H), 1.05 (d, J = 6.6 Hz, 6H).

Part B

8-Bromo-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and 4-*tert*-butylbenzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. Recrystallization from isopropanol followed by chromatography on silica gel (7% methanol in CH_2Cl_2) afforded 8-(4-*tert*-butylphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. >250°C.

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.21 (s, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 8.8, 2.1 Hz, 1H), 7.70-7.67 (m, 3H), 7.52 (dt, J = 8.6, 2.1 Hz, 2H), 6.68

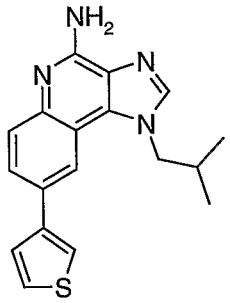
(s, 2H), 4.49 (d, J = 7.2 Hz, 2H), 2.28 (septet, J = 6.8 Hz, 1H), 1.33 (s, 9H), 0.97 (d, J = 6.6 Hz, 6H);

^{13}C NMR (125 MHz, d_6-DMSO) δ 152.2, 149.4, 144.3, 143.4, 137.6, 132.7, 131.7, 128.5, 126.7, 126.2, 125.8, 125.5, 118.0, 115.1, 53.5, 34.2, 31.1, 28.5, 19.4;

Anal. Calcd for $C_{24}H_{28}N_4$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.17; H, 7.57; N, 14.99.

Example 12

1-Isobutyl-8-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



8-Bromo-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and thiophene-3-boronic acid were coupled according to the general procedure described in Part J of Example 1. Recrystallization from isopropanol followed by chromatography on silica gel (7% methanol in CH_2Cl_2) afforded 1-isobutyl-8-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. 235-236°C.

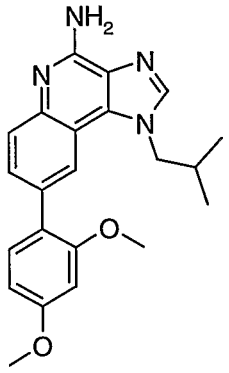
^{1}H NMR (400 MHz, d_6-DMSO) δ 8.20 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.88 (dd, J = 3.0, 1.4 Hz, 1H), 7.81 (dd, J = 8.7, 2.0 Hz, 1H), 7.70 (dd, J = 5.1, 3.0 Hz, 1H), 7.64-7.62 (m, 2H), 6.66 (s, 2H), 4.51 (d, J = 7.4 Hz, 2H), 2.23 (septet, J = 6.9 Hz, 1H), 0.96 (d, J = 6.6 Hz, 6H);

^{13}C NMR (125 MHz, d_6-DMSO) δ 152.1, 144.2, 143.4, 141.8, 131.7, 128.5, 128.1, 127.2, 126.6, 126.1, 125.3, 119.9, 117.5, 115.0, 53.5, 28.4, 19.4;

Anal. Calcd for $C_{18}H_{18}N_4S$: C, 67.05; H, 5.63; N, 17.38. Found: C, 66.74; H, 5.46; N, 17.32.

Example 13

8-(2,4-Dimethoxyphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



8-Bromo-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and 2,4-dimethoxybenzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. Purification by chromatography on silica gel (7% methanol in CH_2Cl_2) afforded 8-(2,4-dimethoxyphenyl)-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. 223-227°C.

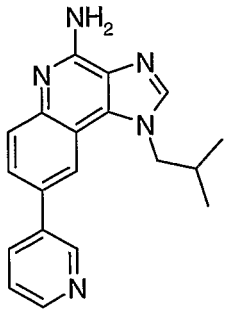
^{1}H NMR (400 MHz, d_6-DMSO) δ 8.18 (s, 1H), 8.08 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.52 (dd, J = 8.6, 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.66 (dd, J = 8.3, 2.4 Hz, 1H), 6.61 (s, 2H), 4.36 (d, J = 7.5 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.34-2.24 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H);

^{13}C NMR (100 MHz, d_6-DMSO) δ 159.8, 157.1, 152.0, 143.6, 143.2, 131.7, 130.9, 130.5, 128.3, 128.1, 125.7, 122.5, 120.8, 114.4, 105.4, 99.0, 55.6, 55.3, 55.4, 28.2, 19.3;

Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.92; H, 6.41; N, 14.67.

Example 14

1-Isobutyl-8-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



8-Bromo-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and pyridine-3-boronic acid were coupled according to the general procedure described in Part J of Example 1. Purification by chromatography on silica gel (7%-10% methanol in CH_2Cl_2 gradient) afforded 1-isobutyl-8-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. 244-246°C.

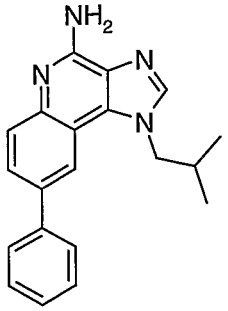
^{1}H NMR (400 MHz, d_6-DMSO) δ 9.01 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.57 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.22 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.18 (ddd, *J* = 8.0, 2.5, 1.6 Hz, 1H), 7.82 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.52 (ddd, *J* = 8.0, 4.7, 0.8 Hz, 1H), 6.76 (s, 2H), 4.52 (d, *J* = 7.2 Hz, 2H), 2.29-2.22 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H);

^{13}C NMR (125 MHz, d_6-DMSO) δ 152.5, 147.9, 147.6, 144.8, 143.5, 135.9, 133.8, 131.7, 129.5, 128.5, 126.9, 125.5, 123.9, 118.7, 115.2, 53.4, 28.4, 19.4;

Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07. Found: C, 71.73; H, 5.91; N, 21.86.

Example 15

1-Isobutyl-8-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



8-Bromo-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and benzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. Recrystallization from isopropanol followed by recrystallization from methanol afforded 1-isobutyl-8-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a beige solid, m.p. 203-204°C.

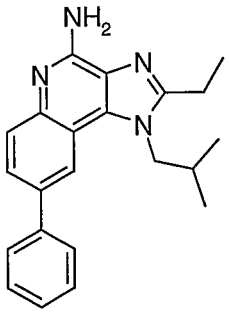
^{1}H NMR (400 MHz, d_6-DMSO) δ 8.21 (s, 1H), 8.17 (d, *J* = 2.0 Hz, 1H), 7.78-7.76 (m, 3H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.52-7.48 (m, 2H), 7.36 (tt, *J* = 7.4, 1.2 Hz, 1H), 6.71 (s, 2H), 4.49 (d, *J* = 7.4 Hz, 2H), 2.32-2.21 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 6H);

^{13}C NMR (100 MHz, d_6-DMSO) δ 152.3, 144.4, 143.4, 140.5, 132.8, 131.8, 129.0, 128.5, 126.9, 126.7, 126.5, 125.6, 118.4, 115.1, 53.6, 28.5, 19.4;

Anal. Calcd for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.80; H, 6.26; N, 17.68.

Example 16

2-Ethyl-1-isobutyl-8-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

To a solution of 2-ethyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (805 mg, 3.00 mmol) in acetic acid (10 mL) was added Br_2 (719 mg, 4.50 mmol), and after 20 h, the resulting solid was collected by filtration and washed with H_2O. The orange solid was suspended in $NaHSO_3$ (25 mL of a saturated solution) and stirred for 23 h, after which it was again collected and stirred with $NaHCO_3$ (20 mL of a saturated solution) and CH_2Cl_2. The organic layer was drawn off, washed with H_2O, dried (Na_2SO_4), filtered, and concentrated to afford 858 mg of a yellow solid. Purification on silica gel (5%-7% MeOH in CH_2Cl_2 gradient) afforded 450 mg of 8-bromo-2-ethyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow solid. Additional purification on silica as before followed by recrystallization from boiling isopropanol (10 mL) afforded 316 mg of white needles, m.p. 222-223°C.

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.02 (s, 1H), 7.52 (s, 2H), 6.65 (s, 2H), 4.33 (d, J = 7.0 Hz, 2H), 2.94 (q, J = 7.5 Hz, 2H), 2.18-2.07 (m, 1H), 1.37 (t, J = 7.5 Hz, 3H), 0.94 (d, J = 6.8 Hz, 6H);

^{13}C NMR (100 MHz, d_6-DMSO) δ 155.1, 152.1, 143.6, 131.4, 128.9, 128.3, 127.0, 122.3, 116.2, 112.8, 51.3, 28.9, 20.2, 19.2, 12.1;

Anal. Calcd for $C_{16}H_{19}BrN_4$: C, 55.34; H, 5.52; N, 16.13. Found: C, 55.26; H, 5.36; N, 16.14.

Part B

8-Bromo-2-ethyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and benzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. Chromatography on silica gel (5%-7% methanol in CH_2Cl_2 gradient) afforded 2-ethyl-1-isobutyl-8-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. 233-235°C.

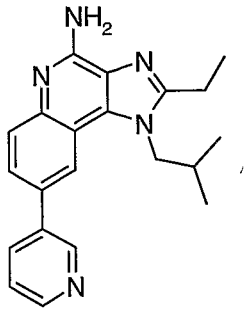
^{1}H NMR (400 MHz, d_6-DMSO) δ 8.15 (d, J = 1.8 Hz, 1H), 7.77-7.72 (m, 3H), 7.68 (d, J = 8.6 Hz, 1H), 7.52-7.48 (m, 2H), 7.36 (tt, J = 7.4, 1.1 Hz, 1H), 6.57 (s, 2H), 4.42 (d, J = 6.6 Hz, 2H), 2.96 (q, J = 7.5 Hz, 2H), 2.35-2.24 (m, 1H), 1.39 (t, J = 7.5 Hz, 3H), 0.98 (d, J = 6.6 Hz, 6H);

^{13}C NMR (100 MHz, d_6-DMSO) δ 154.6, 151.9, 144.2, 140.7, 132.7, 132.5, 129.0, 126.9, 126.8, 126.6, 125.1, 118.2, 115.1, 51.5, 28.9, 20.2, 19.3, 12.1;

Anal. Calcd for $C_{22}H_{24}N_4$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.52; H, 6.89; N, 16.30.

Example 17

2-Ethyl-1-isobutyl-8-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



8-Bromo-2-ethyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and pyridine-3-boronic acid were coupled according to the general procedure described in Part J of Example 1. Chromatography on silica gel (5%-7% methanol in CH_2Cl_2 gradient) followed by recrystallization from isopropanol afforded 2-ethyl-1-isobutyl-8-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as white crystals, m.p. >250°C.

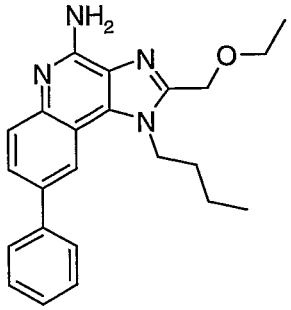
^{1}H NMR (400 MHz, d_6-DMSO) δ 9.00 (d, *J* = 2.4 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.16 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.53 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.63 (s, 2H), 4.45 (d, *J* = 6.8 Hz, 2H), 2.96 (q, *J* = 7.5 Hz, 2H), 2.33-2.23 (m, 1H), 1.39 (t, *J* = 7.5 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 6H);

^{13}C NMR (100 MHz, d_6-DMSO) δ 154.7, 152.2, 147.9, 147.6, 144.7, 136.1, 133.9, 132.4, 129.4, 127.0, 126.9, 125.1, 124.0, 118.6, 115.2, 51.4, 28.9, 20.3, 19.3, 12.1;

Anal. Calcd for $C_{21}H_{23}N_5$: C, 73.02; H, 6.71; N, 20.27. Found: C, 73.24; H, 6.77; N, 20.65.

Example 18

1-Butyl-2-ethoxymethyl-8-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

1-Butyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine was brominated according to the general procedure described in Part A of Example 11. Purification on silica gel (6%-10% methanol in CH_2Cl_2) followed by recrystallization from isopropanol afforded 8-bromo-1-butyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as yellow needles, m.p. 182-183°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.2 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.44 (s, 2H), 4.80 (s, 2H), 4.56-4.51 (m, 2H), 3.61 (q, *J* = 7.0 Hz, 2H), 2.02-1.93 (m, 2H), 1.57 (sextet, *J* = 7.4 Hz, 2H), 1.25 (t, *J* = 6.9 Hz, 3H), 1.07 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 149.7, 144.0, 133.3, 130.6, 129.1, 127.3, 122.7, 117.0, 115.5, 66.6, 65.4, 46.2, 32.3, 20.3, 15.3, 13.9;

MS *m/z* ($M+1^+$) calcd 379.1, obsd 379.0;

Anal. Calcd for $C_{17}H_{21}BrN_4O$: C, 54.12; H, 5.61; N, 14.85. Found: C, 54.01; H, 5.50; N, 14.83.

Part B

8-Bromo-1-butyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and benzeneboronic acid were coupled according to the general procedure described in Part J of Example 1. Chromatography on silica gel (10% methanol in CH_2Cl_2) followed by recrystallization from isopropanol afforded 1-butyl-2-ethoxymethyl-8-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white solid, m.p. 186-187°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 1.9 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.79 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.69-7.66 (m, 2H), 7.52-7.47 (m, 2H), 7.37 (tt, *J* = 7.3, 1.3 Hz, 1H), 5.46 (s, 2H), 4.82 (s, 2H), 4.64-4.58 (m, 2H), 3.62 (q, *J* = 7.0 Hz, 2H), 2.11-2.01 (m, 2H), 1.58 (sextet, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.3 Hz, 3H);

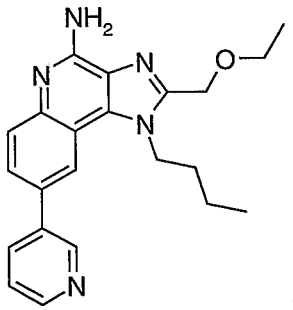
^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 149.2, 144.7, 141.5, 135.4, 134.5, 129.1, 127.8, 127.3, 127.2, 126.9, 118.5, 115.9, 66.5, 65.4, 46.4, 32.5, 20.4, 15.3, 13.9;

MS *m/z* ($M+1^+$) calcd 375.2, obsd 375.2;

Anal. Calcd for $C_{23}H_{26}N_4O$: C, 73.77; H, 7.00; N, 14.96. Found: C, 73.76; H, 7.15; N, 14.95.

Example 19

1-Butyl-2-ethoxymethyl-8-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



8-Bromo-1-butyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and pyridine-3-boronic acid were coupled according to the general procedure described in Part J of Example 1. Chromatography on silica gel (8%-10% methanol in CH_2Cl_2 gradient) followed by recrystallization from isopropanol (3x) and chromatography as above afforded 1-butyl-2-ethoxymethyl-8-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, m.p. 220-222°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.63 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.17 (d, *J* = 2.2 Hz, 1H), 7.96 (ddd, *J* = 7.8, 2.5, 1.6 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.76 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.42 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 5.47 (s, 2H), 4.83 (s, 2H), 4.65-4.60 (m, 2H), 3.63 (q, *J* = 7.0 Hz, 2H),

2.10-1.99 (m, 2H), 1.57 (sextet, J = 7.5 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H);

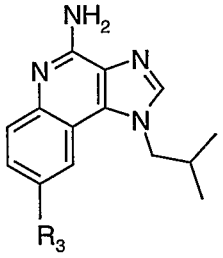
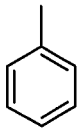
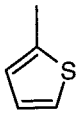
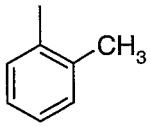
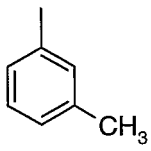
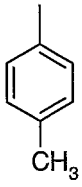
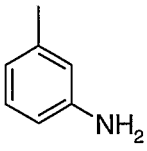
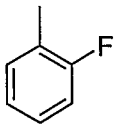
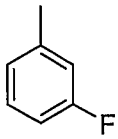
^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 149.5, 148.49, 148.51, 145.2, 137.0, 134.4, 134.3, 131.8, 128.3, 127.4, 126.6, 123.9, 118.7, 116.2, 66.6, 65.4, 46.5, 32.5, 20.4, 15.3, 14.0;

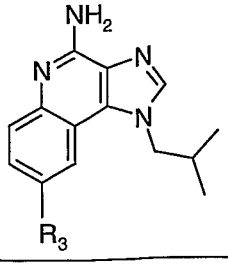
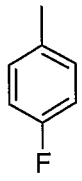
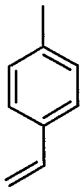
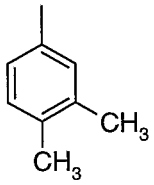
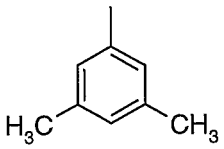
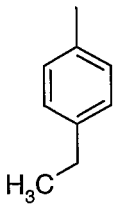
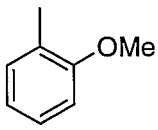
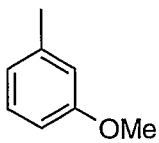
MS *m/z* ($M+1^+$) calcd 376.2, obsd 376.2;

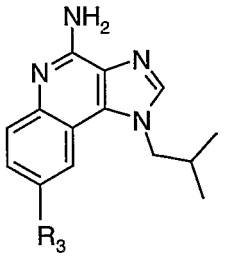
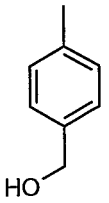
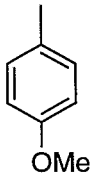
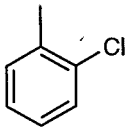
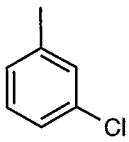
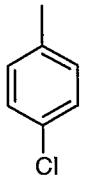
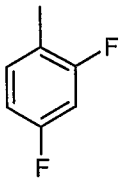
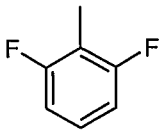
Anal. Calcd for $C_{22}H_{25}N_5O$: C, 70.37; H, 6.71; N, 18.66. Found: C, 70.00; H, 6.49; N, 18.64.

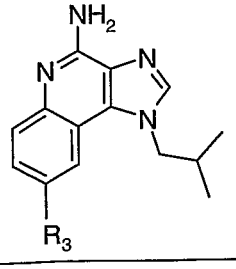
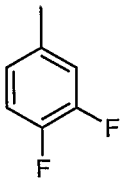
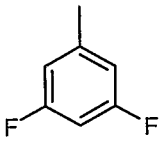
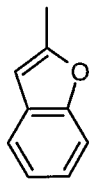
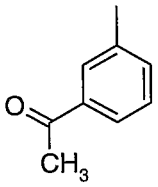
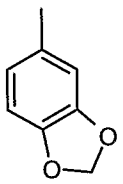
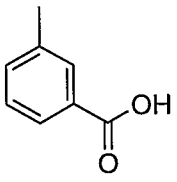
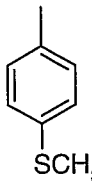
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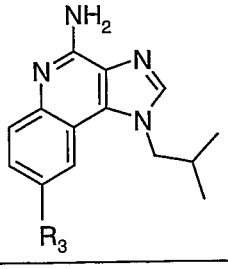
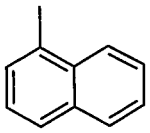
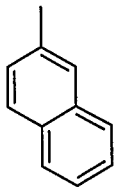
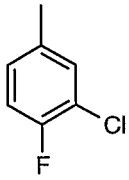
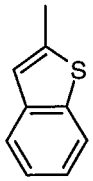
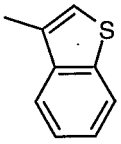
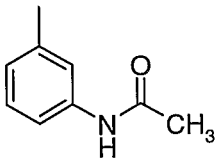
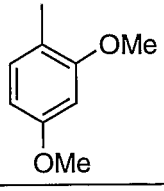
The compounds in the table below were prepared according to the following method. 8-Bromo-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline-4-amine (25 mg) was dissolved in 1:1 volume:volume (v:v) dichloromethane:methanol. An aliquot (2 mL, 1.0 equivalents (eq.)) was placed in a 2 dram (7.4 mL) vial. The solvent was removed by vacuum centrifugation. The vial was charged with the appropriate boronic acid (1.25 eq.), palladium (II) acetate (0.1 eq.), and *n*-propanol (900 µL) and then sonicated for 30 seconds. The vial was then charged with 2M aqueous sodium carbonate solution (313 µL), deionized water (63 µL), and a solution of triphenylphosphine in *n*-propanol (63 µL, 0.15 eq.). The vial was capped and then heated to 80°C for 5 hours in a sand bath. The vial was allowed to cool to room temperature and then the solvent was removed by vacuum centrifugation. The residue was purified by preparative high performance liquid chromatography using the method described above to provide the trifluoroacetate salt of the desired compound. The table below shows the structure of the free base and the measured mass (M + H).

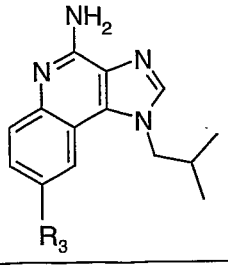
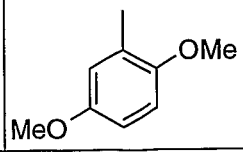
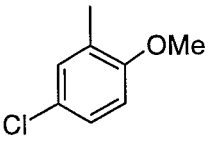
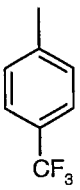
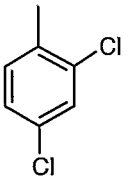
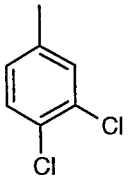
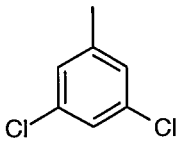
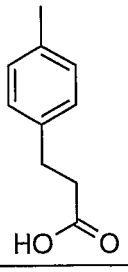
		
Example Number	R_3	Measured Mass (M+H)
20		317.1774
21		323.1330
22		331.1920
23		331.1905
24		331.1945
25		332.1877
26		335.1661
27		335.1678

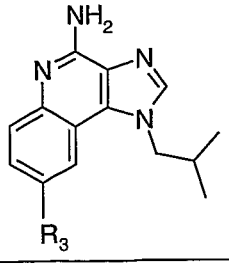
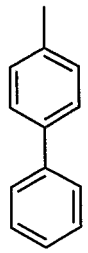
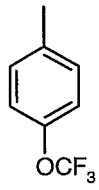
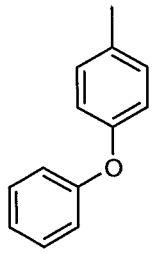
		
Example Number	R_3	Measured Mass (M+H)
28		335.1677
29		343.1921
30		345.2095
31		345.2093
32		345.2099
33		347.1888
34		347.1874

		
Example Number	R_3	Measured Mass (M+H)
35		347.1892
36		347.1865
37		351.1367
38		351.1375
39		351.1375
40		353.1594
41		353.1577

		
Example Number	R_3	Measured Mass (M+H)
42		353.1579
43		353.1587
44		357.1731
45		359.1873
46		361.1670
47		361.1639
48		363.1652

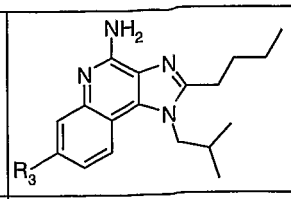
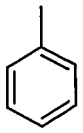
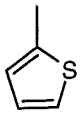
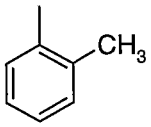
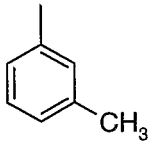
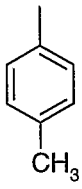
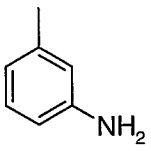
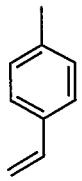
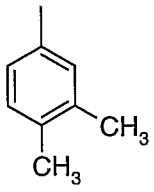
		
Example Number	R_3	Measured Mass (M+H)
49		367.1932
50		367.1942
51		369.1288
52		373.1484
53		373.1494
54		374.1965
55		377.1985

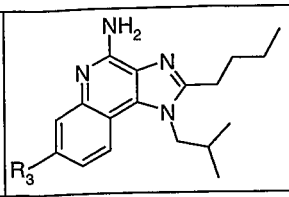
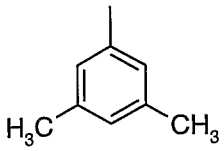
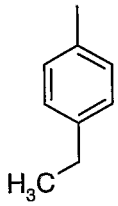
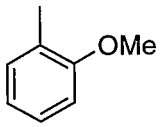
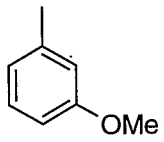
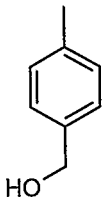
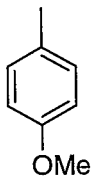
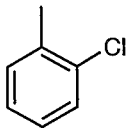
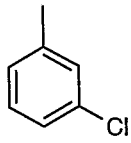
		
Example Number	R_3	Measured Mass (M+H)
56		377.2000
57		381.1507
58		385.1658
59		385.0974
60		385.0998
61		385.0982
62		389.1980

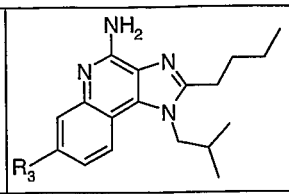
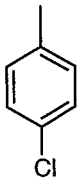
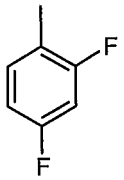
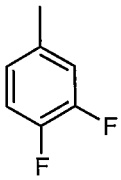
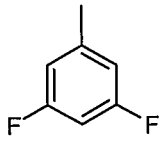
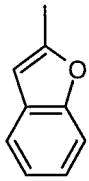
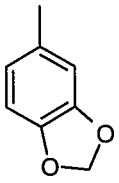
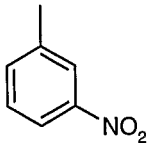
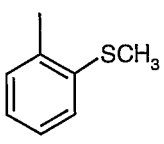
		
Example Number	R_3	Measured Mass (M+H)
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64		401.1596
65		409.2036

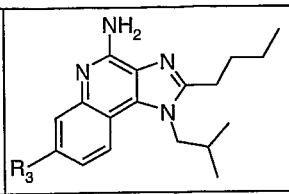
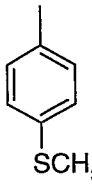
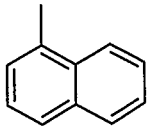
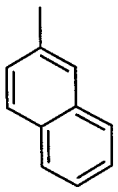
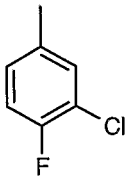
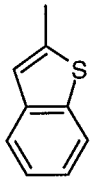
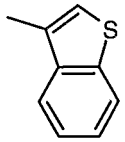
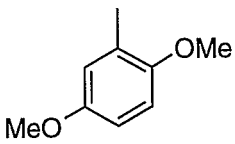
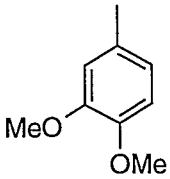
Examples 66–105

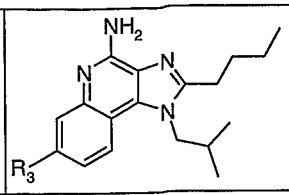
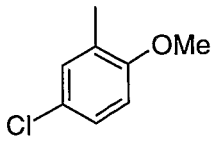
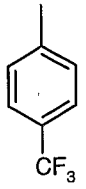
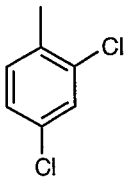
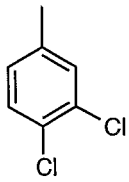
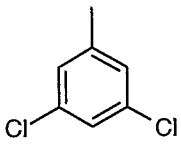
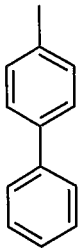
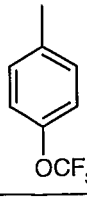
The compounds in the table below were prepared according to the method of Examples 20–65 above using 7-bromo-2-butyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline-4-amine as the starting material. The table below shows the structure of the free base and the measured mass (M + H).

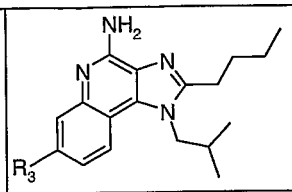
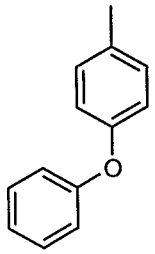
		
Example Number	R_3	Measured Mass (M+H)
66		373.2385
67		379.1978
68		387.2582
69		387.2550
70		387.2545
71		388.2536
72		399.2577
73		401.2712

		
Example Number	R_3	Measured Mass (M+H)
74		401.2686
75		401.2719
76		403.2483
77		403.2507
78		403.2516
79		403.2505
80		407.2021
81		407.2024

		
Example Number	R_3	Measured Mass (M+H)
82		407.2008
83		409.2214
84		409.2227
85		409.2241
86		413.2376
87		417.2313
88		418.2268
89		419.2299

		
Example Number	R_3	Measured Mass (M+H)
90		419.2283
91		423.2552
92		423.2559
93		425.1915
94		429.2125
95		429.2142
96		433.2633
97		433.2613

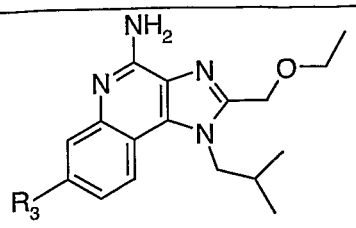
		
Example Number	R_3	Measured Mass (M+H)
98		437.2122
99		441.2265
100		441.1620
101		441.1646
102		441.1586
103		449.2728
104		457.2203

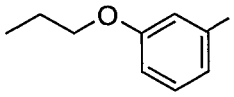
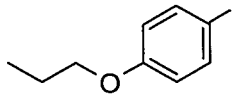
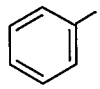
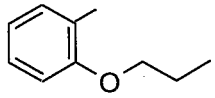
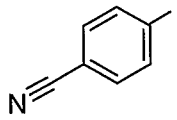
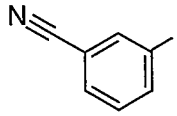
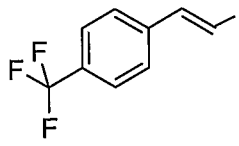
		
Example Number	R_3	Measured Mass (M+H)
105		465.2656

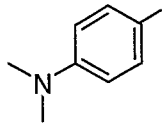
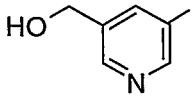
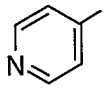
Examples 106-116

7-Bromo-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine and the boronic acid or boronic acid ester from the table below were coupled according to the general procedure described in Part J of Example 1. The reaction was heated at reflux overnight unless otherwise indicated below the table. The solid collected from the reaction was washed with hexanes. Samples that were recrystallized from isopropanol and then dichloromethane:hexanes were dried under high vacuum overnight. Samples that were recrystallized from acetonitrile were then washed with hexanes and dried overnight in a vacuum oven at 75-80 °C. The purification for Examples 115 and 116 is described below the table.

Examples 106-116



Example	Boronic Acid or Ester	Recrystallization Solvent	R_3
106	3-Propoxyphenylboronic acid	Isopropanol then dichloromethane: hexanes	
107	4-Propoxyphenylboronic acid	Isopropanol then dichloromethane: hexanes	
108	Phenylboronic acid	Isopropanol then dichloromethane: hexanes	
109	2-Propoxyphenylboronic acid	Isopropanol, then acetonitrile	
110	4-Cyanophenylboronic acid	Acetonitrile	
111	3-Cyanophenylboronic acid	Acetonitrile	
112	*trans*-2-[4-(Trifluoromethyl)phenyl]vinylboronic acid	Acetonitrile	
113	Pyridine-3-boronic acid 1,3-propanediol cyclic ester	Acetonitrile	

114	4-(Dimethylamino)phenyl boronic acid	Acetonitrile	
115	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	Not used	
116	Pyridine-4-boronic acid pinacol ester	Acetonitrile	

Example 106

2-Ethoxymethyl-1-(2-methylpropyl)-7-(3-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as an off-white powder, mp 140.0-141.0 °C. Anal. Calcd for $C_{26}H_{32}N_4O_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.88; H, 7.36; N, 12.72.

Example 107

2-Ethoxymethyl-1-(2-methylpropyl)-7-(4-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as a white solid, mp 209.0-210.0 °C.

Anal. Calcd for $C_{26}H_{32}N_4O_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.93; H, 7.41; N, 12.76.

Example 108

2-Ethoxymethyl-1-(2-methylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as a white solid, mp 176.5-178.0 °C.

Anal. Calcd for $C_{23}H_{26}N_4O$: C, 73.77; H, 7.00; N, 14.96. Found: C, 73.65; H, 6.90; N, 14.80.

Example 109

2-Ethoxymethyl-1-(2-methylpropyl)-7-(2-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as light-yellow needles, mp 168.0-169.0 °C. Anal. Calcd for $C_{26}H_{32}N_4O_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.96; H, 7.40; N, 13.13.

Example 110

4-(4-Amino-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl)benzonitrile

The product was obtained as an off-white solid, mp 211.0-212.0 °C. Anal. Calcd for $C_{24}H_{25}N_5O$: C, 72.16; H, 6.31; N, 17.53. Found: C, 71.87; H, 6.22; N, 17.40.

Example 111

3-(4-Amino-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl)benzonitrile

The product was obtained as light-brown crystals, mp 210.0-211.0 °C. Anal. Calcd for $C_{24}H_{25}N_5O$: C, 72.16; H, 6.31; N, 17.53. Found: C, 71.88; H, 6.06; N, 17.63.

Example 112

2-Ethoxymethyl-1-(2-methylpropyl)-7-{(E)-2-[(4-trifluoromethyl)phenyl]vinyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as light-yellow needles, mp 193.0-194.0 °C. Anal. Calcd for $C_{26}H_{27}F_3N_4O$: C, 66.65; H, 5.81; N, 11.96. Found: C, 66.51; H, 5.76; N, 11.96.

Example 113

2-Ethoxymethyl-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

Following recrystallization from acetonitrile, the crystals were purified by flash column chromatography on silica gel. The polar component of the

eluent was a mixture of chloroform:methanol:ammonium hydroxide 80:18:2 (CMA). The chromatographic separation was carried out eluting sequentially with 95:5, 90:10, 85:15, 80:20, and 75:25 chloroform:CMA. The fractions containing the product were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure until a precipitate began to form. Hexanes were added, and the resulting solid was isolated by filtration to provide 2-ethoxymethyl-1-(2-methylpropyl)-7-pyridin-3-yl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 179.5-181.5 °C.

Anal. Calcd for $C_{22}H_{25}N_5O$: C, 70.38; H, 6.71; N, 18.65. Found: C, 70.07; H, 6.87; N, 18.57.

Example 114

7-(4-Dimethylaminophenyl)-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as a yellow solid, mp 214.5-215.5 °C.

Anal. Calcd for $C_{25}H_{31}N_5O$: C, 71.91; H, 7.48; N, 16.77. Found: C, 71.66; H, 7.40; N, 16.71.

Example 115

{5-[4-Amino-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyridin-3-yl}methanol

Part A

3-Bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine was prepared according to the published procedure (Zhang, N. et al, *J. Med. Chem.*, *45*, 2832-2840 (2002)). Under a nitrogen atmosphere, a solution of 3-bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine (28.70 g, 94.94 mmol) and triisopropyl borate (26.3 mL, 114 mmol) in dry THF was cooled to -70 °C. *n*-Butyllithium (45.6 mL, 114 mmol) was added dropwise over a period of 1.5 hours. The reaction was stirred for an additional 30 minutes and then allowed to warm to -20 °C. Dilute aqueous ammonium chloride was added, and the mixture was allowed to warm to ambient temperature. The aqueous layer was separated and extracted with diethyl ether. The combined organic fractions were concentrated

under reduced pressure, and methanol was added to the resulting oil. A solid formed, which was stirred with water for two days, isolated by filtration, and dried under reduced pressure to provide 18.19 g of 5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid as a white solid.

Part B

The coupling reaction was heated at reflux for four days, and the product was purified on a Biotage HORIZON High-Performance Flash Chromatography instrument (HPFC) (eluting with chloroform:CMA in a gradient from 100:0 to 55:45.) The fractions containing the product were combined and concentrated under reduced pressure until a precipitate began to form. Hexanes were added, and the resulting solid was isolated by filtration and dried overnight in an oven at 70 °C to provide [5-(4-amino-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl)pyridin-3-yl]methanol as an off-white powder, mp 211.0-212.0 °C.

Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27. Found: C, 68.04; H, 7.07; N, 17.21.

Example 116

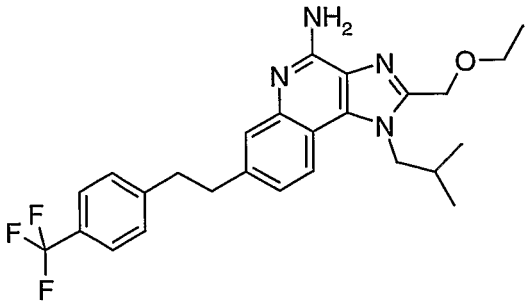
2-Ethoxymethyl-1-(2-methylpropyl)-(7-pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The reaction was heated at reflux for 48 hours, and the reaction mixture was partitioned between aqueous sodium chloride and dichloromethane. The aqueous layer was extracted twice with dichloromethane, and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 80:20) followed by recrystallization from acetonitrile to provide 2-ethoxymethyl-1-(2-methylpropyl)-(7-pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 211-213 °C.

Anal. Calcd for $C_{22}H_{25}N_5O$: C, 70.38; H, 6.71; N, 18.65. Found: C, 70.33; H, 6.76; N, 18.69.

Example 117

2-Ethoxymethyl-1-(2-methylpropyl)-7-{2-[(trifluoromethyl)phenyl]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine



A solution of 2-ethoxymethyl-1-(2-methylpropyl)-7-{(E)-2-[(4-trifluoromethyl)phenyl]vinyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.47 g, 1.0 mmol) in ethyl acetate (200 mL) was added to a Parr vessel charged with 10% palladium on carbon (0.30 g). The reaction was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) for seven days. The reaction mixture was filtered, and the filter cake was washed with ethyl acetate. The filtrate was concentrated under reduced pressure to provide 0.22 g of 2-ethoxymethyl-1-(2-methylpropyl)-7-{2-[(4-trifluoromethyl)phenyl]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, mp 175.5-178 °C.

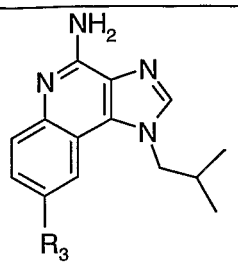
Anal. Calcd for $C_{26}H_{29}F_3N_4O$: C, 66.37; H, 6.21; N, 11.91. Found: C, 66.09; H, 6.39; N, 11.53.

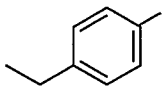
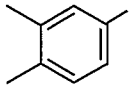
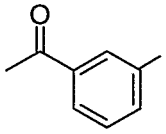
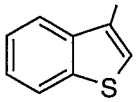
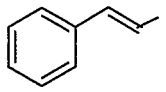
Examples 118-122

For Examples 118-121, triphenylphosphine (31 mg, 0.12 mmol) and palladium (II) acetate (9 mg, 0.04 mmol) were added to a mixture of 8-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.28 g, 4.00 mmol), the boronic acid from the table below (6.00 mmol, 1.5 equivalents), *n*-propanol (7 mL), aqueous sodium carbonate (5.0 mL of 2 M), and water (1.4 mL). The reaction was purged with nitrogen and heated at reflux under a nitrogen atmosphere for one to two hours. Upon cooling to ambient temperature, a solid formed and was isolated by filtration and washed with water. The crude product was recrystallized from methanol and dried overnight at 1.33 Pa and 98 °C to provide the products listed below the table.

For Example 122, 8-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine and the boronic acid from the table below were coupled according to the general procedure described in Part J of Example 1. The reaction was heated at reflux overnight. The crude product was recrystallized from methanol.

Examples 118-122



Example	Boronic acid or ester	R_3
118	4-Ethylphenylboronic acid	
119	3,4-Dimethylphenylboronic acid	
120	3-Acetylphenylboronic acid	
121	Thianaphthene-3-boronic acid	
122	*trans*-2-Phenylvinylboronic acid	

Example 118

8-(4-Ethylphenyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as pale yellow needles, mp 238-240 °C. Anal. Calcd for $C_{22}H_{24}N_4$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.67; H, 7.00; N, 16.31.

Example 119

8-(3,4-Dimethylphenyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as pale yellow needles, mp 204-205 °C.

Anal. Calcd for $C_{22}H_{24}N_4$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.33; H, 7.28; N, 16.21.

Example 120

1-{3-[4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]phenyl}ethanone

The product was obtained as a white solid, mp 217-218 °C.

Anal. Calcd for $C_{22}H_{22}N_4O$: C, 73.72; H, 6.19; N, 15.63. Found: C, 73.87; H, 6.24; N, 15.75.

Example 121

8-Benzo[b]thiophen-3-yl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as pale yellow needles, mp 247-248 °C.

Anal. Calcd for $C_{22}H_{20}N_4S \bullet 0.14\ H_2O$: C, 70.46; H, 5.45; N, 14.94. Found: C, 70.28; H, 5.26; N, 14.91.

Example 122

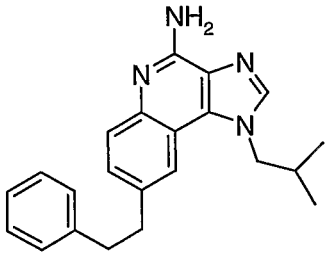
1-(2-Methylpropyl)-8-styryl-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as pale yellow crystals, mp 228-230 °C.

Anal. Calcd for $C_{22}H_{22}N_4 \bullet 1.5H_2O$: C, 71.52; H, 6.82; N, 15.16. Found: C, 71.34; H, 6.63; N, 15.20.

Example 123

1-(2-Methylpropyl)-8-phenethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine

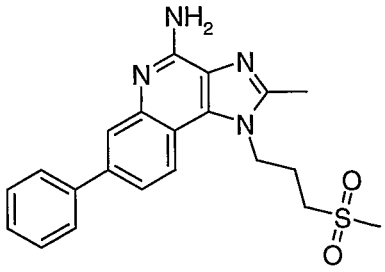


A solution of 1-(2-methylpropyl)-8-styryl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.37 g, 4.00 mmol) in ethanol (40 mL) was added to a Parr vessel charged with 10% palladium on carbon (137 mg). The reaction was placed under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) for six days. The reaction mixture was filtered through a layer of CELITE filter aid, and the filter cake was washed with ethanol. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from methanol to provide 0.300 g of 1-(2-methylpropyl)-8-phenethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 175-178 °C.

Anal. Calcd for $C_{22}H_{24}N_4 \bullet 0.75H_2O$: C, 73.82; H, 7.18; N, 15.65. Found: C, 73.45; H, 7.32; N, 15.33.

Example 124

2-Methyl-1-(3-methanesulfonylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

N^4-(3-Methylsulfanylpropyl)-7-phenylquinoline-3,4-diamine and trimethyl orthoacetate were reacted according to the general method described in Part H of Example 10. The crude product was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) to

provide 2-methyl-1-(3-methanesulfanylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a light brown solid.

Part B

The method described in Part I of Example 10 was followed. The crude product was recrystallized from acetonitrile (67 mL/g) and then from methanol (106 mL/g). The crystals were purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol), and the resulting solid was recrystallized from acetonitrile (220 mL/g) and dried for 17 hours under vacuum at 85 °C to provide 2-methyl-1-(3-methanesulfonylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, mp mp 203-205 °C.

Anal. Calcd for $C_{21}H_{22}N_4O_2S$: C, 63.94; H, 5.62: N, 14.20. Found: C, 63.81; H, 5.47; N, 14.14.

Examples 125-135

Part A

Triethylamine (17.35 mL, 124 mmol) was added to a solution of 7-bromo-4-chloro-3-nitroquinoline (29.84 g, 104 mmol) in dichloromethane (253 mL), and the reaction was cooled to 0 °C. 1-Amino-2-methylpropan-2-ol (10.17 g, 114 mmol) was added dropwise, and then the reaction was allowed to warm to ambient temperature and stirred overnight. A precipitate formed and was isolated by filtration and washed with water. The crude solid was recrystallized from a mixture of isopropanol and acetonitrile to provide 27.78 g of 1-(7-bromo-3-nitroquinolin-4-ylamino)-2-methylpropan-2-ol as a solid.

Part B

A solution of 1-(7-bromo-3-nitroquinolin-4-ylamino)-2-methylpropan-2-ol (27.78 g, 81.66 mmol) in acetonitrile (1.2 L) was added to a Parr vessel charged with 5% platinum on carbon (0.84 g), and the reaction was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) for two days. The reaction mixture was filtered through a layer of CELITE filter aid, and the filter cake was washed with ethanol (1 L). The filtrate was concentrated under reduced pressure to provide 21.70 g of 1-(3-amino-7-bromoquinolin-4-ylamino)-2-methylpropan-2-ol as a yellow oil.

Part C

A solution of 1-(3-amino-7-bromoquinolin-4-ylamino)-2-methylpropan-2-ol (158.19 g, 0.510 mol) in dichloromethane (1.2 L) was cooled to 0 °C. Ethoxyacetyl chloride (62.50 g, 0.510 mol) was added dropwise, and then the reaction was allowed to warm to ambient temperature and stirred overnight. A precipitate formed and was isolated by filtration to provide *N*-[7-bromo-4-(2-hydroxy-2-methylpropylamino)quinolin-3-yl]-2-ethoxyacetamide as a solid.

Part D

A solution of sodium hydroxide (25 g, 0.625 mol) in water (205 mL) was added to a solution of *N*-[7-bromo-4-(2-hydroxy-2-methylpropylamino)quinolin-3-yl]-2-ethoxyacetamide (170.88 g, 0.431 mol) in ethanol (700 mL), and the reaction was heated at reflux under a nitrogen atmosphere for two hours. Upon cooling the reaction, a precipitate formed and was isolated by filtration. The solid was purified by flash column chromatography on silica gel (eluting sequentially with chloroform, 99:1 chloroform:methanol, and 97:3 chloroform:methanol) to provide 80.31 g of 1-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as a tan solid.

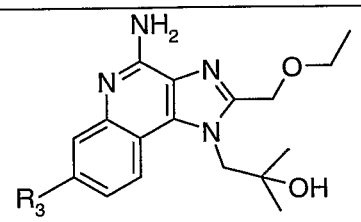
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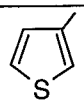
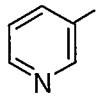
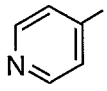
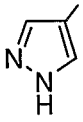
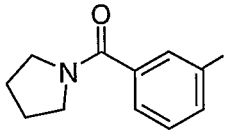
3-Chloroperoxybenzoic acid (73.27 g of 50% pure material, 0.212 mol) was added in four portions over a period of 30 minutes to a solution of 1-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (80.31 g, 0.212 mol) in dichloromethane (950 mL), and the reaction was stirred overnight at ambient temperature. The reaction mixture was washed twice with aqueous sodium carbonate (2 M) and then diluted with additional dichloromethane (1.5 L total volume). The solution was cooled to 0 °C, and concentrated ammonium hydroxide (83 mL) was added. *p*-Toluenesulfonyl chloride (48.56 g, 0.254 mol) was then added over a period of 20 minutes, and the reaction was allowed to warm to ambient temperature and stirred overnight. A precipitate formed and was isolated by filtration and washed sequentially with 2 M aqueous sodium carbonate and water. The crude product was recrystallized from 2:1 isopropanol:acetonitrile and collected in two crops to provide 58.4 g of 1-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as a solid.

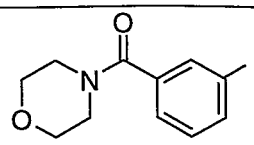
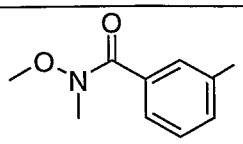
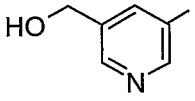
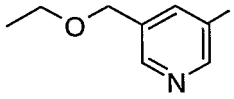
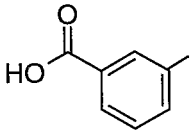
Part F

1-(4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol and the boronic acid or boronic acid ester from the table below were coupled according to the general procedure described in Part J of Example 1. The reaction was heated at reflux for between 1.5 and 27 hours. The reaction mixture was partitioned between brine and chloroform. The aqueous layer was extracted twice with chloroform, and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The purification and characterization of each compound is given below the table.

Examples 125-135



Example	Boronic acid or ester	R_3
125	Thiophene-3-boronic acid	
126	Pyridine-3-boronic acid 1,3-propanediol cyclic ester	
127	Pyridine-4-boronic acid pinacol ester	
128	1*H*-Pyrazole-4-boronic acid pinacol ester	
129	3-(Pyrrolidine-1-carbonyl)phenylboronic acid	

130	3-(Morpholine-4-carbonyl)phenylboronic acid	
131	Phenylboronic acid	
132	4-(*N,O*-Dimethylhydroxylaminocarbonyl)phenyl boronic acid	
133	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	
134	5-Ethoxymethylpyridin-3-ylboronic acid	
135	3-Carboxyphenylboronic acid	

Example 125

1-[4-Amino-2-ethoxymethyl-7-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was recrystallized from 2-butanone and then purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 90:10 to 65:35). The resulting solid was recrystallized from acetonitrile to provide 1-[4-amino-2-ethoxymethyl-7-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as white crystals, mp 204-205 °C.

Anal. Calcd for $C_{21}H_{24}N_4O_2S$: C, 63.61; H, 6.10; N, 14.13. Found: C, 63.71; H, 6.23; N, 14.31.

Example 126

1-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified three times by HPFC (eluting with chloroform:CMA in a gradient from 90:10 to 70:30). The resulting solid was recrystallized from acetonitrile and dried overnight at 1.33 Pa and 98 °C to provide 1-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white solid, mp 197-199 °C.

Anal. Calcd for $C_{22}H_{25}N_5O_2 \bullet 0.28H_2O$: C, 66.63; H, 6.50; N, 17.66. Found: C, 66.63; H, 6.55; N, 17.88.

Example 127

1-[4-Amino-2-ethoxymethyl-7-(pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified twice by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 55:45). The fractions containing the pure product were concentrated under reduced pressure until a precipitate formed. Hexanes were added, and the resulting solid was isolated by filtration and dried overnight under vacuum to provide 1-[4-amino-2-ethoxymethyl-7-(pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a pale yellow solid, mp 220-221 °C.

Anal. Calcd for $C_{22}H_{25}N_5O_2 \bullet 0.39\ H_2O$: C, 66.31; H, 6.52; N, 17.57. Found: C, 65.95; H, 6.32; N, 17.44.

Example 128

1-[4-Amino-2-ethoxymethyl-7-(1*H*-pyrazol-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 40:60) followed by recrystallization from methanol to provide 1-[4-amino-2-ethoxymethyl-7-(1*H*-pyrazol-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as white, granular crystals, mp >250 °C.

Anal. Calcd for $C_{20}H_{24}N_6O_2$: C, 63.14; H, 6.36; N, 22.09. Found: C, 62.89; H, 6.35; N, 21.94.

Example 129

{3-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}pyrrolidin-1-ylmethanone

The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 65:35) followed by recrystallizations from isopropanol and acetonitrile to provide {3-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}pyrrolidin-1-ylmethanone as a white powder, mp 216.5-217.5 °C.

Anal. Calcd for $C_{28}H_{33}N_5O_3$: C, 68.97; H, 6.82; N, 14.36. Found: C, 68.67; H, 7.01; N, 14.42.

Example 130

{3-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}morpholin-4-ylmethanone

The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) followed by recrystallizations from isopropanol, dichloromethane:hexanes, and isopropanol. The crystals were dried under vacuum with heating to provide {3-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}morpholin-4-ylmethanone as a white powder, mp 152.0-154.0 °C.

Anal. Calcd for $C_{28}H_{33}N_5O_4 \bullet 0.5\ H_2O$: C, 65.61; H, 6.69; N, 13.66. Found: C, 65.67; H, 7.09; N, 13.72.

Example 131

1-(4-Amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol

The crude product was recrystallized from methanol:water and then purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) to provide 1-(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as a white solid, mp 211-212°C.

^{1}H NMR (500 mHz, DMSO-d_6) δ 8.34 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 2 Hz, 1H), 7.76-7.73 (m, 2H), 7.52-7.46 (m, 3H), 7.38-7.35 (m, 1H), 6.58 (br s, 2H), 4.88 (s, 3H), 4.68 (br s, 2H), 3.52 (q, J = 7 Hz, 2H), 1.19 (br s, 6H), 1.13 (t, J = 7 Hz, 3H);

HRMS (ESI) *m/z* 391.2124 (391.2134 calcd for $C_{23}H_{26}N_4O_2$, (M + H).

Example 132

4-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-*N*-methoxy-*N*-methylbenzamide

The crude product was purified three times by HPFC (eluting with chloroform:CMA in gradients from 100:0 to 70:30). The fractions containing the pure product were concentrated under reduced pressure until a precipitate formed. Hexanes were added, and the resulting solid was isolated by filtration and dried overnight in a vacuum oven at 80 °C and then heated to melting under vacuum to provide 4-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-*N*-methoxy-*N*-methylbenzamide as a light green solid.

^{13}C NMR (75 MHz, DMSO-d_6) δ 168.7, 152.3, 151.0, 145.5, 141.9, 137.0, 133.9, 133.0, 128.5, 126.2, 123.7, 122.2, 119.1, 114.8, 70.6, 65.2, 64.8, 60.7, 54.8, 33.2, 27.6, 14.9;

HRMS (EI) *m/z* 478.2446 (478.2454 calcd for $C_{26}H_{31}N_5O_4$).

Example 133

1-[4-Amino-2-ethoxymethyl-7-(5-hydroxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The reaction was heated at reflux for three hours and then allowed to cool and stand at ambient temperature for several days. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 65:35). The solid (3.73 g) was dissolved in tetrahydrofuran (THF) (5 mL), water (5 mL), and acetic acid (15 mL). The solution was allowed to stand at room temperature for three days, and then the solvents were removed under reduced pressure. The residue was partitioned between chloroform and 2 M aqueous

sodium carbonate:brine, and the aqueous layer was extracted with chloroform (7 x). The combined organic fractions were concentrated under reduced pressure. The residue was then purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 35:65) followed by recrystallization from acetonitrile to provide 1-[4-amino-2-ethoxymethyl-7-(5-hydroxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white powder, mp 188-190 °C.

Anal. Calcd for $C_{23}H_{27}N_5O_3$: C, 65.54; H, 6.46; N, 16.62. Found: C, 65.22; H, 6.66; N, 16.56.

Example 134

1-[4-Amino-2-ethoxymethyl-7-(5-ethoxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

Part A

(5-Bromopyridin-3-yl)methanol was prepared according to the published procedure (Zhang, N. et al, *J. Med. Chem.*, *45*, 2832-2840 (2002)). A solution of (5-bromopyridin-3-yl)methanol (7.39 g, 39.3 mmol) in THF was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (39.3 mL of a 1.0 M solution in THF) was added, and the reaction was stirred for 20 minutes. Iodoethane (3.46 mL, 43.2 mmol) and DMF were added, and the reaction was allowed to warm to ambient temperature and stirred overnight. Brine was added, and the aqueous layer was extracted twice with hexanes. The combined organic fractions were concentrated under reduced pressure, and the residue was purified by HPFC (eluting with hexanes:ethyl acetate in a gradient from 100:0 to 70:30) to provide 5.11 g of 3-bromo-5-ethoxymethylpyridine as a colorless oil.

Part B

The method described in Part A of Example 115 was used to convert 3-bromo-5-ethoxymethylpyridine (5.11 g, 23.6 mmol) to 5-ethoxymethylpyridin-3-ylboronic acid, which was obtained as a white solid.

Part C

The crude product from the coupling reaction was recrystallized from dichloromethane:hexanes and then purified twice by HPFC (eluting with

chloroform:CMA in a gradient from 100:0 to 70:30). The resulting solid was recrystallized from dichloromethane:hexanes to provide 1-[4-amino-2-ethoxymethyl-7-(5-ethoxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white powder, mp 156.0 - 156.5 °C.

Anal. Calcd for $C_{25}H_{31}N_5O_3$: C, 66.79; H, 6.95; N, 15.58. Found: C, 66.46; H, 6.98; N, 15.51.

Example 135

3-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]benzoic acid

The crude product was isolated as a solid from the reaction mixture, recrystallized from dimethyl sulfoxide, stirred with methanol:water, and isolated by filtration to provide 3-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]benzoic acid as a white powder, mp > 250 °C.

HRMS (ESI) *m/z* 435.2016 (435.2032 calcd for $C_{24}H_{26}N_4O_4$, (M + H).

Examples 136-141

Part A

The method described in Part A of Example 9 was used to react 1-(3-amino-7-bromoquinolin-4-ylamino)-2-methylpropan-2-ol (29.0 g, 93.5 mmol) with 3-methoxypropionyl chloride (11.5 g, 93.5 mmol). The crude product was recrystallized from 2:1 ethyl acetate:hexane and then purified by flash column chromatography on silica gel (eluting sequentially with 60:40 acetone:toluene and acetone). The resulting solid was recystallized from 3:1 ethyl acetate hexane to provide 13.3 g of 1-[7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as translucent crystals.

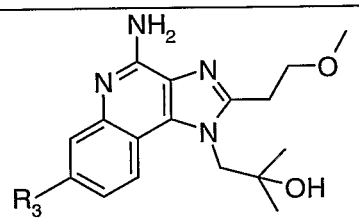
Part B

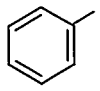
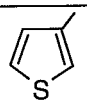
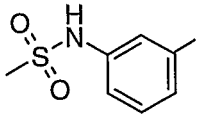
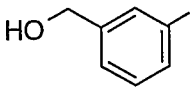
1-[7-Bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol was oxidized and then aminated according to the methods described in Parts H and I of Example 1. After recrystallization from ethanol, 1-[4-amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol was obtained as a pale orange solid.

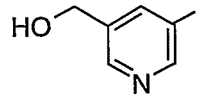
Part C

1-[4-Amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol and the boronic acid or boronic acid ester from the table below were coupled according to the general procedure described in Part J of Example 1. The reaction was heated at reflux for between three hours and overnight. For Example 136, a solid formed upon cooling to room temperature and was isolated by filtration and washed with hexanes. For Examples 137-141, the reaction mixture was partitioned between brine and chloroform. The aqueous layer was extracted twice with chloroform, and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The purification and characterization of each compound is given below the table.

Examples 136-141



Example	Boronic acid or ester	R_3
136	Phenylboronic acid	
137	Thiophene-3-boronic acid	
138	Pyridine-3-boronic acid 1,3-propanediol cyclic ester	
139	3-(Methylsulfonylamino)phenylboronic acid	
140	3-(Hydroxymethyl)phenylboronic acid	

141	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	

Example 136

1-[4-Amino-2-(2-methoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was recrystallized twice from isopropanol and then from dichloromethane:hexanes and dried overnight under vacuum to provide 1-[4-amino-2-(2-methoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white solid, mp 226-227 °C.

Anal. Calcd for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.49; H, 6.56; N, 14.28.

Example 137

1-[4-Amino-2-(2-methoxyethyl)-7-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 85:15 to 70:30). The resulting solid was recrystallized from ethanol to provide 1-[4-amino-2-(2-methoxyethyl)-7-(thiophen-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as white crystals, mp 233-234 °C.

Anal. Calcd for $C_{21}H_{24}N_4O_2S$: C, 63.61; H, 6.10; N, 14.13. Found: C, 63.45; H, 6.21; N, 14.07.

Example 138

1-[4-Amino-2-(2-methoxyethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 90:10 to 70:30). The resulting solid was recrystallized from methanol to provide 1-[4-amino-2-(2-methoxyethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as white needles, mp 158-160 °C.

Anal. Calcd for $C_{22}H_{25}N_5O_2 \bullet 1.10H_2O$: C, 64.26; H, 6.67; N, 17.03. Found: C, 64.12; H, 7.02; N, 17.27.

Example 139

N-{3-[4-Amino-1-(2-hydroxy-2-methylpropyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}methanesulfamide

The crude product was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 90:10 to 80:20) to provide *N*-{3-[4-amino-1-(2-hydroxy-2-methylpropyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}methanesulfamide as a white powder, mp 156-158 °C.

Anal. Calcd for $C_{24}H_{29}N_5O_4S \cdot \bullet 3.0\ H_2O$: C, 53.62; H, 6.56; N, 13.03. Found: C, 53.50; H, 6.49; N, 12.95.

Example 140

1-[4-Amino-7-(3-hydroxymethylphenyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 90:10 to 80:20) to provide 1-[4-amino-7-(3-hydroxymethylphenyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white powder, mp 212-213 °C.

Anal. Calcd for $C_{24}H_{28}N_4O_3 \bullet 0.17\ H_2O$: C, 68.06; H, 6.74; N, 13.22. Found: C, 67.73; H, 6.63; N, 13.04.

Example 141

1-[4-Amino-7-(5-hydroxymethylpyridin-3-yl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 90:10 to 80:20) to provide 1-[4-amino-7-(5-hydroxymethylpyridin-3-yl)-2-(2-methoxyethyl)-1*H*-

imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a yellow solid, mp 210-211 °C.

Anal. Calcd for $C_{23}H_{27}N_5O_3 \bullet 1.0\ H_2O$: C, 62.85; H, 6.65; N, 15.93. Found: C, 62.47; H, 6.33; N, 15.83.

Examples 142-144

Part A

Triethyl orthopropionate (12.9 g, 73.2 mmol) and pyridine hydrochloride (220 mg) were added to a solution of 1-(3-amino-7-bromoquinolin-4-ylamino)-2-methylpropan-2-ol (22.1 g, 70.6 mmol) in anhydrous toluene (300 mL), and the reaction was heated at reflux for three hours. The reaction was allowed to cool to ambient temperature and stand overnight; a precipitate formed. The precipitate was isolated by filtration, washed with toluene, and air-dried to provide 18.42 g of 1-(7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as beige crystals.

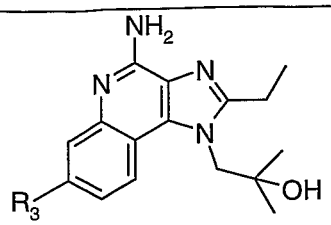
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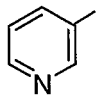
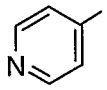
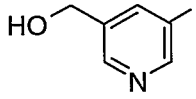
1-(7-Bromo-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The product from amination was isolated by filtration from the reaction mixture and stirred with 2 M aqueous sodium carbonate and chloroform for ten minutes. The resulting solid was isolated by filtration and washed with water to provide 1-(4-amino-7-bromo-2-methoxyethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as a white solid, which was used without further purification.

Part C

1-(4-Amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol and the boronic acid or boronic acid ester from the table below were coupled according to the general procedure described in Part J of Example 1. The reaction was heated at reflux between 12 and 54 hours. The work-up procedure described in Part F of Examples 125-131 was followed, and the purification and characterization of each compound is described below the table.

Examples 142-144



Example	Boronic acid or ester	R_3
142	Pyridine-3-boronic acid 1,3-propanediol cyclic ester	
143	Pyridine-4-boronic acid pinacol ester	
144	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	

Example 142

1-[4-Amino-2-ethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 55:45). The resulting solid was dissolved in chloroform and precipitated with hexane, recrystallized twice from acetonitrile, and finally recystallized from 3:1 acetonitrile:methanol and dried at 1.33 Pa and 80 °C to provide 1-[4-amino-2-ethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as white needles, mp 245-247 °C. Anal. Calcd for $C_{21}H_{23}N_5O$: C, 69.78; H, 6.41; N, 19.38. Found: C, 69.60; H, 6.53; N, 19.58.

Example 143

1-[4-Amino-2-ethyl-7-(pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 65:35) The resulting solid was recrystallized from

acetonitrile:methanol and air-dried to provide 1-[4-amino-2-ethyl-7-(pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white solid, mp >250 °C.

Anal. Calcd for $C_{21}H_{23}N_5O$: C, 69.78; H, 6.41; N, 19.38. Found: C, 69.68; H, 6.54; N, 19.43.

Example 144

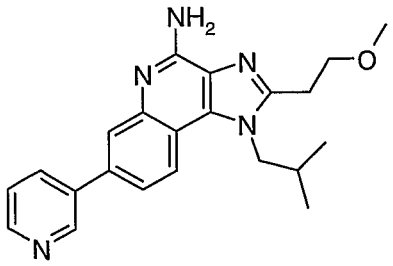
1-[4-Amino-2-ethyl-7-(5-hydroxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified by HPFC, and the resulting solid was dissolved in THF (5 mL), water (5 mL), and acetic acid (15 mL). The solution was allowed to stand at room temperature for three days, and 5 M aqueous sodium hydroxide and 2 M aqueous sodium carbonate were added to adjust to pH 11. A solid was present and was isolated by filtration and purified by HPFC™ (eluting with chloroform:CMA in a gradient from 100:0 to 35:65). The resulting solid was recrystallized from 3:1 methanol:acetonitrile and dried overnight at 1.33 Pa and 80 °C to provide 1-[4-amino-2-ethyl-7-(5-hydroxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as white crystals, mp >250 °C.

Anal. Calcd for $C_{22}H_{25}N_5O_2$: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.28; H, 6.71; N, 18.06.

Example 145

2-(2-Methoxyethyl)-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



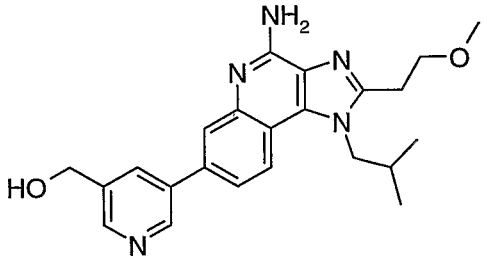
7-Bromo-2-(2-methoxyethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine was prepared according to the procedures described in Parts

A and B of Example 9 using methoxypropanoyl chloride instead of ethoxyacetyl chloride. 7-Bromo-2-(2-methoxyethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine was coupled with pyridine-3-boronic acid 1,3-propanediol cyclic ester according to the method described in Examples 118-121. The reaction was heated at reflux overnight, and the work-up procedure described in Part F of Examples 125-131 was followed. The crude product was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 90:10 to 76:24) followed by recrystallization from methanol. The crystals were dried at 1.33 Pa and 98 °C to provide 2-(2-methoxyethyl)-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as white needles, mp 207-208 °C.

Anal. Calcd for $C_{22}H_{25}N_5O$: C, 70.38; H, 6.71; N, 18.65. Found: C, 70.31; H, 6.76; N, 18.76.

Example 146

{5-[4-Amino-2-(2-methoxyethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyridin-3-yl}methanol



7-Bromo-2-(2-methoxyethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine was coupled with 5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid according to the method described in Examples 118-121. The reaction was heated at reflux for 2.25 hours, and the work-up procedure described in Part F of Examples 125-131 was followed. The crude product was purified and deprotected according to the procedure described in Example 144. The resulting solid was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 55:45) followed by recrystallization from acetonitrile to provide {5-[4-amino-2-(2-methoxyethyl)-1-

(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyridin-3-yl}methanol as white needles, mp 202-204 °C.

Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27. Found: C, 67.89; H, 6.62; N, 17.26.

Examples 147-150

Part A

6-Bromo-4-chloro-3-nitroquinoline, prepared from 4-bromoaniline according to the methods described in Parts A-D of Example 1, was treated according to the methods described in Parts A and B of Examples 125-135 to provide 1-(3-amino-6-bromoquinolin-4-ylamino)-2-methylpropan-2-ol.

Part B

1-(3-Amino-6-bromoquinolin-4-ylamino)-2-methylpropan-2-ol was treated according to the method described in Parts A and B of Example 9 to provide 1-(4-amino-8-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol.

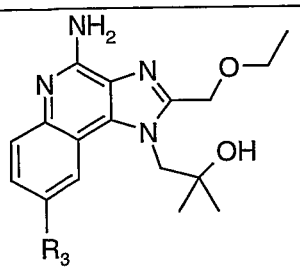
Part C

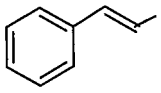
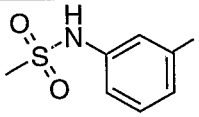
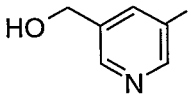
1-(4-Amino-8-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol and the boronic acid or boronic acid ester from the table below were coupled according to the general procedure described in Part J of Example 1. The reaction was stirred overnight. The crude product was purified by flash column chromatography on silica gel (eluting sequentially with 95:5 and 90:10 dichloromethane:methanol) followed by recrystallization from methanol to provide the products shown in the table below.

For Example 150, the product from the coupling reaction (1.5 g, 2.8 mmol) was dissolved in THF (25 mL). Tetrabutylammonium fluoride (3.64 mL of a 1.0 M solution in THF) was added, and the reaction was stirred for one hour at ambient temperature. Saturated ammonium chloride (20 mL) was added, and the aqueous layer was separated and extracted with dichloromethane (3 x 50 mL). The combined organic fractions were dried over sodium sulfate and filtered. A precipitate formed in the filtrate and was isolated by filtration. The solid was washed with dichloromethane, stirred with methanol, isolated by

filtration, and washed with methanol to provide the product shown in the table below.

Examples 147-150



Example	Boronic Acid or Ester	R_3
147	*trans*-2-Phenylvinylboronic acid	
148	Pyridine-3-boronic acid	
149	3-(Methylsulfonylamino)phenylboronic acid	
150	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	

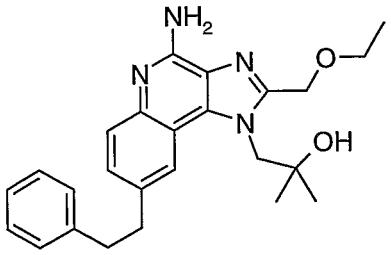
Examples 147-150

Example	Name	Form	mp (°C)	Anal.
147	1-(4-Amino-2-ethoxymethyl-8-styryl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	Pale yellow powder	217-218	Calcd for $C_{25}H_{28}N_4O_2$: C, 72.09; H, 6.78; N, 13.45. Found: C, 71.71; H, 6.97; N, 13.46.

148	1-[4-Amino-2-ethoxymethyl-8-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White crystals	222-223	Calcd for $C_{22}H_{25}N_5O_2$: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.23; H, 6.55; N, 17.85.
149	*N*-{3-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]phenyl}methanesulfamide	Off-white crystals	221-222	Calcd for $C_{24}H_{29}N_5O_4S \bullet 0.33H_2O$: C, 58.89; H, 6.11; N, 14.31. Found: C, 58.81; H, 5.80; N, 14.30.
150	1-[4-Amino-2-ethoxymethyl-8-(5-hydroxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White powder	230-232	Calcd for $C_{23}H_{27}N_5O_3$: C, 65.54; H, 6.46; N, 16.62. Found: C, 65.25; H, 6.24; N, 16.65.

Example 151

1-(4-Amino-2-ethoxymethyl-8-phenethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol



1-(4-Amino-2-ethoxymethyl-8-styryl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (1.0 g, 2.4 mmol) was treated according to the method described in Example 123. The crude product was purified by flash column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) prior to recrystallization from methanol to provide 0.500 g of 1-(4-amino-2-ethoxymethyl-8-phenethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as white crystals, mp 175-176 °C.

Anal. Calcd for $C_{25}H_{30}N_4O_2$: C, 70.38; H, 7.30; N, 13.13. Found: C, 70.27; H, 7.26; N, 13.11.

Examples 152-156

Part A

A solution of *tert*-butoxy *N*-(4-aminobutyl)carbamate (15.38 g, 81.7 mmol) in dichloromethane (100 mL) was added dropwise over a period of 30 minutes to a solution of 7-bromo-4-chloro-3-nitroquinoline (74.3 mmol) and triethylamine (20.6 mL, 149 mmol) in dichloromethane (400 mL), and the reaction was stirred overnight at ambient temperature. The reaction was diluted with dichloromethane (500 mL), washed sequentially with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was recrystallized from isopropanol to provide *tert*-butyl [4-(7-bromo-3-nitroquinolin-4-ylamino)butyl]carbamate as a yellow solid.

Part B

A solution of sodium hydrosulfite (43.35 g, 249 mmol) and potassium carbonate (38.28 g, 277 mmol) in water (300 mL) was added to a mixture of *tert*-butyl [4-(7-bromo-3-nitroquinolin-4-ylamino)butyl]carbamate (24.3 g, 55.3 mmol) and 1,1'-diethyl-4,4'-bipyridinium dibromide (1.03 g, 2.76 mmol) in dichloromethane (368 mL) and water (40 mL), and the reaction was stirred overnight at ambient temperature. The reaction mixture was filtered through a layer of CELITE filter aid. The aqueous filtrate was extracted with dichloromethane, and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 22.4 g of *tert*-butyl [4-(3-amino-7-bromoquinolin-4-ylamino)butyl]carbamate as a brown powder.

Part C

tert-Butyl [4-(3-amino-7-bromoquinolin-4-ylamino)butyl]carbamate (24.3 g, 59.4 mmol) was treated with ethoxyacetyl chloride (7.28 g, 59.4 mmol) according to the method described in Part C of Examples 125-135.

Part D

A solution of the material from Part C and triethylamine (33.1 mL, 238 mmol) in ethanol (295 mL) was heated at reflux for two hours. The reaction was

then allowed to cool to ambient temperature, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, and the resulting solution was washed sequentially with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluting sequentially with 90:10 and 85:15 chloroform:CMA) to provide 23.6 g of *tert*-butyl [4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate as a tan solid.

Part E

Concentrated hydrochloric acid (15.6 mL, 0.194 mol) was added to a solution of *tert*-butyl [4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate (23.2 g, 48 mmol) in ethanol, and the reaction was heated at reflux for 20 minutes. A precipitate formed, and the reaction was allowed to cool to ambient temperature overnight. The solid was isolated by filtration, washed with ethanol, and dissolved in water. The solution was washed with dichloromethane and then made basic with the addition of 50% aqueous sodium hydroxide. The basic solution was extracted with dichloromethane (3 x 300 mL), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 17 g of 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butylamine as an off-white solid.

Part F

3-Chloropropanesulfonyl chloride (5.45 mL, 44.8 mmol) was added dropwise over a period of four minutes to a solution of 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butylamine (16.9 g, 44.8 mmoL) and triethylamine (9.42 mL, 67.6 mmol) in dichloromethane (300 mL), and the reaction was stirred at ambient temperature for 30 minutes. The reaction was poured into water, and the organic layer was washed with brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was dissolved in *N,N*-dimethylformamide (DMF) (300 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (10.1 mL, 67.6 mmol) was added. The reaction was stirred overnight at ambient temperature under a nitrogen atmosphere. Additional DBU (5 mL) was added, and the reaction was stirred for

an additional four hours. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane. The resulting solution was washed with water (2 x 200 mL) and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 7-bromo-1-[4-(1,1-dioxidoisothiazolidin-2-yl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline as an oil.

Part G

7-Bromo-1-[4-(1,1-dioxidoisothiazolidin-2-yl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation was carried out in chloroform, and several equivalents of 3-chloroperoxybenzoic acid were used. The product from amination was purified by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 98:2 to 85:15) followed by recrystallization from acetonitrile to provide 7-bromo-1-[4-(1,1-dioxidoisothiazolidin-2-yl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid.

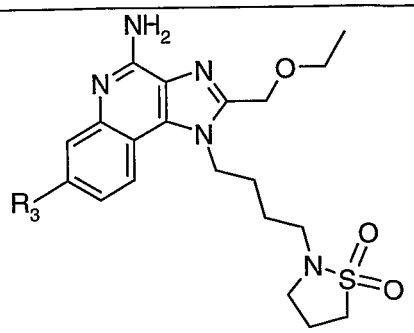
Part H

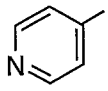
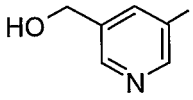
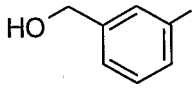
7-Bromo-1-[4-(1,1-dioxidoisothiazolidin-2-yl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and the boronic acid or boronic acid ester from the table below were coupled according to the general procedure described in Part J of Example 1. The reaction was heated at reflux until an analysis by HPLC indicated the reaction was complete. The work-up procedure described in Part F of Examples 125-135 was followed, and the crude product was purified by column chromatography on silica gel (eluting with a gradient of chloroform:CMA) followed by recrystallization using the solvent indicated in the table below.

For Example 155, the reaction was heated at reflux for three hours. Following chromatographic purification, the residue was deprotected according to the method described in Example 144, purified by column chromatography, and recrystallized from acetonitrile.

For Example 156, the coupling was carried out using tri(*ortho*-tolyl)phosphine instead of triphenylphosphine.

Examples 152-156



Example	Boronic acid or ester	Recrystallization solvent	R_3
152	Phenylboronic acid	Acetonitrile	
153	Pyridine-3-boronic acid 1,3-propanediol cyclic ester	Isopropanol	
154	Pyridine-4-boronic acid pinacol ester	Methanol then Isopropanol	
155	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	Acetonitrile	
156	3-(Hydroxymethyl)phenylboronic acid	Acetonitrile (twice)	

Example 152

1-[4-(1,1-Dioxidoisothiazolidin-2-yl)butyl]-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as white crystals, mp 167-168.5 °C.

^{13}C NMR (75MHz, DMSO-d_6) δ 152.3, 148.9, 145.6, 140.1, 138.5, 132.8, 129.0, 127.4, 126.7, 126.4, 123.8, 121.0, 120.1, 113.8, 65.4, 64.1, 46.5, 46.1, 45.1, 43.8, 27.2, 24.3, 18.3, 14.9;

MS (APCI) *m/z* 494.2213 (494.2226 calcd for $C_{26}H_{31}N_5O_3S$, M+H);

Anal. Calcd for $C_{26}H_{31}N_5O_3S$: C, 63.26; H, 6.33; N, 14.19; S, 6.50. Found: C, 62.66; H, 6.34; N, 14.10; S, 6.45.

Example 153

1-[4-(1,1-Dioxidoisothiazolidin-2-yl)-butyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as white, flocculent crystals, mp 171-173 °C.

Anal. Calcd for $C_{25}H_{30}N_6O_3S$: C, 60.71; H, 6.11; N, 16.99. Found: C, 60.56; H, 6.18; N, 16.92.

Example 154

1-[4-(1,1-Dioxidoisothiazolidin-2-yl)-butyl]-2-ethoxymethyl-7-(pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as a white, crystalline solid, mp 186-187.5 °C.

Anal. Calcd for $C_{25}H_{30}N_6O_3S$: C, 60.71; H, 6.11; N, 16.99; S, 6.48. Found: C, 60.36; H, 6.38; N, 16.88; S, 6.42.

Example 155

(5-{4-Amino-1-[4-(1,1-dioxidoisothiazolidin-2-yl)butyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl}pyridin-3-yl)methanol

The product was obtained as a white, powdery solid, mp 184.5-186 °C.

Anal. Calcd for $C_{26}H_{32}N_6O_4S$: C, 59.52; H, 6.15; N, 16.02; S, 6.11. Found: C, 59.53; H, 6.01; N, 16.06; S, 6.04.

Example 156

(5-{4-Amino-1-[4-(1,1-dioxidoisothiazolidin-2-yl)butyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl}phenyl)methanol

The product was obtained as a white powder, mp 158-161 °C.

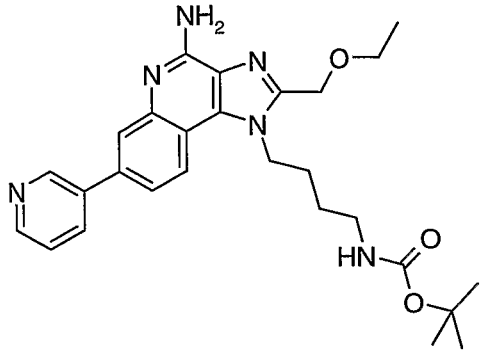
^{13}C NMR (75MHz, DMSO-d_6) δ 152.3, 148.9, 145.4, 143.3, 139.9, 138.7, 132.9, 128.7, 126.3, 125.5, 125.0, 124.8, 123.6, 121.0, 120.1, 113.7, 65.4, 64.1, 62.9, 46.5, 46.1, 45.1, 43.8, 27.2, 24.3, 18.3, 14.9;

MS (APCI) *m/z* 524.2 (524.2 calcd for $C_{27}H_{33}N_5O_4S$, M+H);

Anal. Calcd for $C_{27}H_{33}N_5O_4S \bullet 0.3H_2O$: C, 61.93; H, 6.35; N, 13.37; S, 6.12. Found: C, 61.51; H, 6.78; N, 13.24; S, 6.12.

Example 157

tert-Butyl {4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate

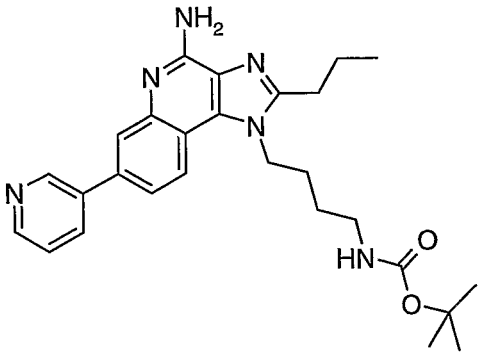


tert-Butyl [4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate was oxidized and aminated according to the methods described in Parts H and I of Example 1 to afford *tert*-butyl [4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate, which was coupled with 3-pyridylboronic acid according to the method described in Part J of Example 1. The reaction was heated at reflux for four hours, and the work-up procedure described in Part F of Examples 125-135 was followed. The crude product was recrystallized from acetonitrile (1 mL/g) to provide *tert*-butyl {4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate as a white solid, mp 117-119 °C.

Anal. Calcd for $C_{27}H_{34}N_6O_3$: C, 64.33; H, 7.10; N, 16.67. Found: C, 64.35; H, 7.42; N, 16.71.

Example 158

tert-Butyl {4-[4-amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate



tert-Butyl [4-(3-amino-7-bromoquinolin-4-ylamino)butyl]carbamate was treated with butyryl chloride and cyclized according to the methods described in Part C and D of Examples 125-135. The resulting product, *tert*-butyl [4-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate was oxidized and aminated according to the methods described in Parts H and I of Example 1 to afford *tert*-butyl [4-(4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate, which was coupled with 3-pyridylboronic acid according to the method described in Part J of Example 1. The reaction was heated at reflux for four hours, and the work-up procedure described in Part F of Examples 125-135 was followed. The crude product was recrystallized from toluene (1 mL/g) to provide *tert*-butyl {4-[4-amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate as a tan powder, mp 136-138 °C.

Anal. Calcd for $C_{27}H_{34}N_6O_2$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.92; H, 7.61; N, 16.92.

Examples 159-161

Part A

7-Bromo-4-chloro-3-nitroquinoline (39.85 g, 138.6 mmol) was reacted with 2,2-dimethyl-1,3-dioxolane-4-methanamine (20.0 g, 152 mmol) according to the method described in Part A of Examples 125-135 to provide 48.35 g of (7-bromo-3-nitroquinolin-4-yl)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl)amine as a yellow solid. The product was not recrystallized.

Part B

The methods described in Parts B, C, and D of Examples 152-156 were used to convert (7-bromo-3-nitroquinolin-4-yl)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl)amine to 7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline, which was obtained as an off-white solid, mp 138-140 °C. In Part B, 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide was used instead of 1,1'-diethyl-4,4'-bipyridinium dibromide. Triethylamine (1.1 equivalents) was added in Part C.

Anal. Calcd for $C_{19}H_{22}BrN_3O_3$: C, 54.30; H, 5.28; N, 10.00. Found: C, 54.07; H, 5.25; N, 9.90.

Part C

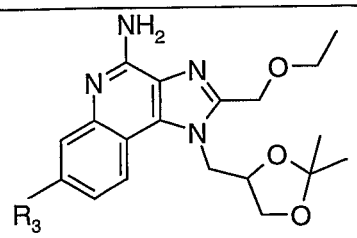
7-Bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized. The product from amination was purified by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 85:15) followed by recrystallization from acetonitrile to provide 7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 174-175 °C.

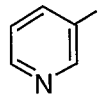
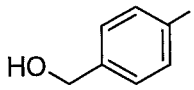
Anal. Calcd for $C_{19}H_{23}BrN_4O_3$: C, 52.42; H, 5.33; N, 12.87. Found: C, 52.41; H, 5.25; N, 12.81.

Part D

7-Bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and the boronic acid or ester from the table below were coupled according to the method described in Examples 118-121. The work-up procedure described in Part F of Examples 125-135 was followed. For Examples 159 and 160, the crude product was purified by flash chromatography (eluting with a gradient of chloroform:CMA) followed by recrystallization from the solvent indicated in the table below. For Example 161, the crude product was dissolved in hot methanol, filtered, concentrated under reduced pressure, triturated with ethyl acetate, isolated by filtration, and then recrystallized from methanol.

Examples 159-161



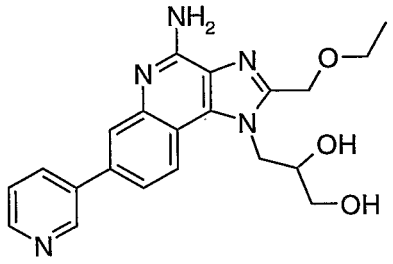
Example	Boronic acid or ester	Recrystallization solvent	R_3
159	Pyridine-3-boronic acid 1,3-propanediol cyclic ester	Acetonitrile (twice)	
160	4-(Hydroxymethyl)phenylboronic acid	Ethanol	
161	Phenylboronic acid	Methanol	

Example	Name	Form	mp	Anal.
159	1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White crystals	181-182 °C	Calcd for $C_{24}H_{27}N_5O_3$: C, 65.65; H, 6.33; N, 15.95. Found: C, 65.77; H, 6.33; N, 15.96.
160	1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(4-hydroxymethylphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white crystals	219-220 °C	Calcd for $C_{26}H_{30}N_4O_4$: C, 67.51; H, 6.54; N, 12.11. Found: C, 67.47; H, 6.21; N, 11.98.

161	1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-phenyl-1H-imidazo[4,5-c]quinolin-4-amine	Light yellow crystals	168-170 °C	Calcd for $C_{25}H_{28}N_4O_3$: C, 69.42; H, 6.53; N, 12.95. Found: C, 69.37; H, 6.62; N, 13.04.

Example 162

3-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propane-1,2-diol



Hydrochloric acid (12 mL of 1 N) was added to a solution of 1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.75 g, 1.73 mmol) in THF, and the reaction was stirred overnight at ambient temperature. The THF was removed under reduced pressure, and 1% aqueous sodium hydroxide was added to the remaining solution to adjust to pH 9. A precipitate formed, was isolated by filtration, washed with water, and dried in an oven at 60 °C to provide 0.61 g of 3-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propane-1,2-diol as a white solid, mp 218-220 °C.

Anal. Calcd for $C_{21}H_{23}N_5O_3$: C, 62.68; H, 6.01; N, 17.40. Found: C, 62.58; H, 5.99; N, 17.29.

Examples 163-175

Part A

7-Bromo-4-chloro-3-nitroquinoline (29.54 g, 102.7 mmol) was reacted with 3-methoxy propyl amine (10.07 g, 113.0 mmol) according to the method described in Part A of Examples 125-135 to provide 32.9 g of (7-bromo-3-

nitroquinolin-4-yl)-(3-methoxypropyl)amine as a yellow solid. The product was not recrystallized.

Part B

The methods described in Parts B, C, and D of Examples 152-156 were used to convert (7-bromo-3-nitroquinolin-4-yl)-(3-methoxypropyl)amine to 7-bromo-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline, which was obtained as a white solid. In Part B, 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide was used instead of 1,1'-diethyl-4,4'-bipyridinium dibromide. Triethylamine (1.1 equivalents) was added in Part C. The chromatographic purification in Part D was carried out using ethyl acetate:acetone as the eluent.

Part C

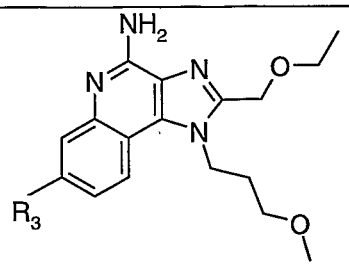
7-Bromo-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized. The product from amination was purified as described in Part C of Examples 159-161 to provide 7-bromo-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as off-white crystals.

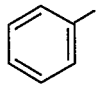
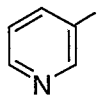
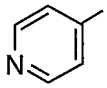
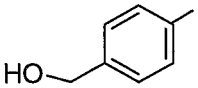
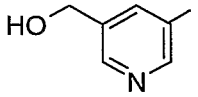
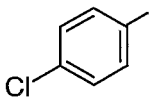
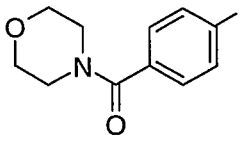
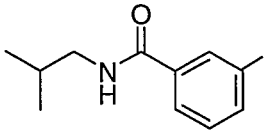
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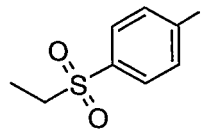
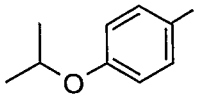
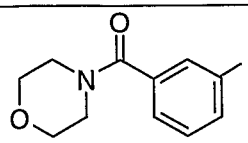
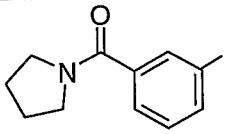
7-Bromo-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine and the boronic acid or ester from the table below were coupled according to the method described in Examples 118-121 or in Part J of Example 1. For Example 159, the product was isolated as a solid and recrystallized from ethanol. For the remaining examples, the crude product was purified by flash chromatography (eluting with a gradient of chloroform:CMA) followed by recrystallization from the solvent indicated in the table below.

For Example 167, following chromatographic purification the product was deprotected according to the method described in Example 144. The crude deprotected product was recrystallized from isopropanol and then from acetonitrile to provide the product shown in the table below.

Examples 163-175



Ex.	Boronic acid or ester	Recrystallization solvent	R_3
163	Phenylboronic acid	Isopropanol then acetonitrile	
164	Pyridine-3-boronic acid 1,3-propanediol cyclic ester	Acetonitrile (twice)	
165	Pyridine-4-boronic acid pinacol ester	Ethanol (twice)	
166	4-(Hydroxymethyl)phenylboronic acid	Ethanol	
167	5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid	Isopropanol then Acetonitrile	
168	Furan-2-boronic acid	Acetonitrile	
169	4-Chlorophenylboronic acid	Ethanol (twice)	
170	4-(Morpholine-4-carbonyl)phenylboronic acid	Ethanol	
171	3-(iso-Butylaminocarbonyl) phenylboronic acid	Ethanol (twice)	

172	4-(Ethylsulfonyl)phenylboronic acid	Ethanol	
173	4-(iso-Propoxyphenyl)boronic acid	Acetonitrile	
174	3-(Morpholine-4-carbonyl)phenylboronic acid	Acetonitrile	
175	3-(Pyrrolidine-1-carbonyl)phenylboronic acid	Ethyl acetate	

Examples 163-175

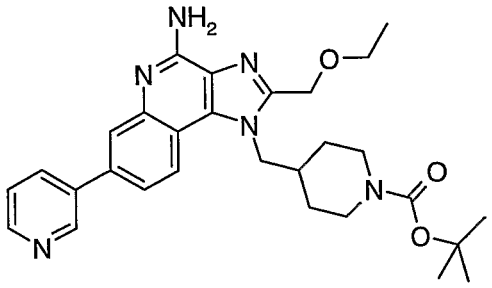
Example	Name	Form	Mp (C°)	Anal.
163	2-Ethoxymethyl-1-(3-methoxypropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White crystals	146-147	Calcd for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.73; H, 6.70; N, 14.34.
164	2-Ethoxymethyl-1-(3-methoxypropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White crystals	151-152	Calcd for $C_{22}H_{25}N_5O_2$: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.21; H, 6.46; N, 17.97.
165	2-Ethoxymethyl-1-(3-methoxypropyl)-7-(pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White, crystalline solid	225-226	Calcd for $C_{22}H_{25}N_5O_2$: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.29; H, 6.37; N, 17.64.
166	2-Ethoxymethyl-1-(3-methoxypropyl)-7-(4-hydroxymethylphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White, crystalline solid	228-229	Calcd for $C_{24}H_{28}N_4O_3$: C, 68.55; H, 6.71; N, 13.32. Found: C, 68.36; H, 6.86; N, 13.06.
167	2-Ethoxymethyl-1-(3-methoxypropyl)-7-(5-hydroxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	198-199	Calcd for $C_{23}H_{27}N_5O_3$: C, 65.54; H, 6.46; N, 16.62. Found: C, 65.41; H, 6.40; N, 16.63.
168	2-Ethoxymethyl-7-(furan-2-yl)-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white solid	144-145	Calcd for $C_{21}H_{24}N_4O_3$: C, 66.30; H, 6.36; N, 14.73. Found: C, 65.96; H, 6.16; N, 14.56.

169	7-(4-Chlorophenyl)-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	188-190	Calcd for $C_{23}H_{25}ClN_4O_2$: C, 65.01; H, 5.93; N, 13.18. Found: C, 64.72; H, 5.93; N, 13.04.
170	{4-[4-Amino-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}morpholin-4-ylmethanone	White solid	163-165	Calcd for $C_{28}H_{33}N_5O_4$: C, 66.78; H, 6.61; N, 13.91. Found: C, 66.52; H, 6.59; N, 13.71.
171	3-[4-Amino-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-*N*-(2-methylpropyl)benzamide	Off-white solid	209-210	Calcd for $C_{28}H_{35}N_5O_3$: C, 68.69; H, 7.21; N, 14.30. Found: C, 68.52; H, 7.44; N, 14.23.
172	7-[(4-Ethanesulfonyl)phenyl]-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	156-158	Calcd for $C_{25}H_{30}N_4O_4S$: C, 62.22; H, 6.27; N, 11.61. Found: C, 61.99; H, 5.98; N, 11.47.
173	2-Ethoxymethyl-7-[4-(2-propoxy)phenyl]-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white crystals	175-177	Calcd for $C_{26}H_{32}N_4O_3$: C, 69.62; H, 7.19; N, 12.49. Found: C, 69.70; H, 7.45; N, 12.60.
174	{3-[4-Amino-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}morpholin-4-ylmethanone	Off-white crystals	174-176	Calcd for $C_{28}H_{33}N_5O_4$: C, 66.78; H, 6.61; N, 13.91. Found: C, 66.55; H, 6.53; N, 13.97.

175	{3-[4-Amino-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}pyrrolidin-1-ylmethanone	White solid	145-146	Calcd for $C_{28}H_{33}N_5O_3 \bullet 0.85HCl$: C, 64.85; H, 5.81; N, 6.58. Found: C, 64.90; H, 5.74; N, 6.61.

Example 176

tert-Butyl 4-{[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate



Part A

7-Bromo-4-chloro-3-nitroquinoline was treated according to the methods described in Parts A through D of Examples 152-156 using 1-(*tert*-butoxycarbonyl)-4-(aminomethyl)piperidine (Carceller, E. et al, *J. Med. Chem.*, *39*, 487-493 (1996)) in Part A. In Part B, 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide was used instead of 1,1'-diethyl-4,4'-bipyridinium dibromide. Triethylamine (1.1 equivalents) was added to the reaction in Part C. Following chromatographic purification in Part D (eluting with 95:5 chloroform:CMA), *tert*-butyl 4-[(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate was obtained as an off-white solid. A small portion of the product was recrystallized from acetonitrile to provide a white solid, mp 169-170 °C.

Anal. Calcd for $C_{24}H_{31}BrN_4O_3$: C, 57.26; H, 6.21; N, 11.13. Found: C, 57.31; H, 6.29; N, 11.07.

Part B

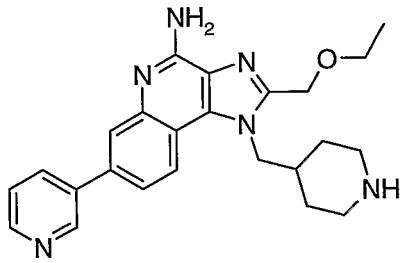
tert-Butyl 4-[(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized. The product from amination was purified as described in Part C of Examples 159-161 to provide *tert*-butyl 4-[(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate as a tan solid.

Part C

tert-Butyl 4-[(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate (12.79 g, 24.67 mmol) and pyrdine-3-boronic acid 1,3-propanediol cyclic ester (4.42 g, 27.14 mmol) were coupled according to the method described in Examples 118-121. The work-up procedure described in Part F of Examples 125-135 was followed. The crude product was recrystallized twice from ethyl acetate to provide 10.89 g of *tert*-butyl 4-{[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate as an off-white solid, mp 197-198 °C. Anal. Calcd for $C_{29}H_{36}N_6O_3 \cdot 0.5\ H_2O$: C, 66.26; H, 7.10; N, 15.99. Found: C, 66.47; H, 7.47; N, 16.00.

Example 177

2-Ethoxymethyl-1-(piperidin-4-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride

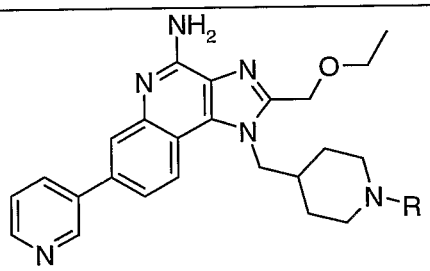


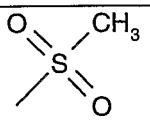
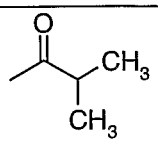
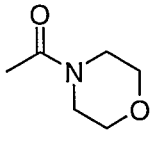
Ethanolic hydrochloric acid (17.68 mL of 4.25 M) was added to a solution of *tert*-butyl 4-{[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate (9.71 g, 18.8 mmol) in anhydrous ethanol, and the reaction was heated at reflux for two hours. A precipitate formed, and the reaction was allowed to cool to ambient temperature. The solid was isolated by filtration, washed with a small volume of cold ethanol, and dried under reduced pressure to provide 7.1 g of 2-ethoxymethyl-1-(piperidin-4-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride as an off-white solid, mp > 250 °C. Anal. Calcd for $C_{24}H_{28}N_6O \cdot 3\ HCl \cdot 1.17\ H_2O$: C, 52.70; H, 6.14; N, 15.36. Found: C, 53.11; H, 6.48; N, 15.07.

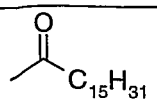
Examples 178-181

A 0.02-0.03 M solution of 2-ethoxymethyl-1-(piperidin-4-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride (1 equivalent) and triethylamine (5 equivalents) in the solvent indicated in the table below was cooled to 4 °C. The reagent from the table below (1 equivalent) was added dropwise, and the reaction was allowed to warm to ambient temperature and stirred for between two and 24 hours. The reaction mixture was diluted with chloroform, and the resulting solution was washed sequentially with water, 4% aqueous sodium carbonate (2 x), water, and brine and then concentrated under reduced pressure. For Examples 178, 179, and 181, the residue was purified by flash column chromatography on silica gel (eluting with chloroform:CMA) followed by recrystallization from the solvent indicated in the table below. For Example 180, the crude product was recystallized from ethyl acetate. The structures of the products are shown in the table.

Examples 178-181



Example	Reagent	Reaction solvent	Recrystallization solvent	R
178	Methanesulfonyl chloride	Chloroform	Acetonitrile then ethyl acetate	
179	Isobutyryl chloride	1-Methyl-2-pyrrolidinone	Ethyl Acetate	
180	4-Morpholinecarbonyl chloride	Chloroform	Ethyl acetate	

181	Palmitoyl chloride	Chloroform	Chloroform:hexanes	

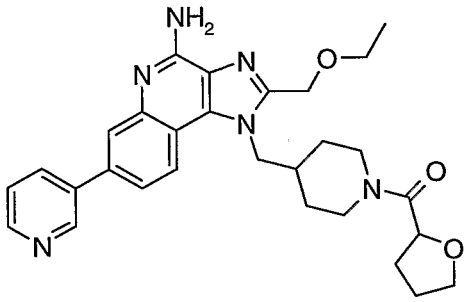
Examples 178-181

Example	Name	Form	Mp (°C)	Anal.
178	2-Ethoxymethyl-1-{[1-(methanesulfonyl)piperidin-4-yl]methyl}-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white powder	254-255	Calcd for $C_{25}H_{30}N_6O_3S$ • 0.4 HCl: C, 58.97; H, 6.02; N, 16.50; Cl, 2.78. Found: C, 58.94; H, 5.78; N, 16.34; Cl, 3.06.
179	2-Ethoxymethyl-1-[(1-isobutyrylpiperidin-4-yl)methyl]-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Beige powder	130-132	Calcd for $C_{28}H_{34}N_6O_2$ • 0.375 H_2O: C, 68.16; H, 7.10; N, 17.03. Found: C, 67.84; H, 7.14; N, 16.82.
180	2-Ethoxymethyl-1-{[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]methyl}-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Tan solid	224-225	Calcd for $C_{29}H_{35}N_7O_3$ • 0.125 H_2O: C, 65.49; H, 6.68; N, 18.43. Found: C, 65.12; H, 6.40; N, 18.19.

181	2-Ethoxymethyl-1-[(1-palmitoylpiperidin-4-yl)methyl]-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white crystalline solid	72-75	Calcd for $C_{40}H_{58}N_6O_2 \cdot 0.1 H_2O$: C, 73.15; H, 8.93; N, 12.80. Found: C, 72.83; H, 8.84; N, 12.75

Example 182

2-Ethoxymethyl-7-(pyridin-3-yl)-1-{[1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine



A solution of 2-ethoxymethyl-1-(piperidin-4-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride (1.0 g, 1.90 mmol) and triethylamine (1.35 mL, 9.50 mmol) in chloroform (80 mL) was cooled to 4 °C. 2-Tetrahydrofuroic acid (0.243 g, 2.09 mmol) and 1-(3-dimethoxyaminopropyl)-3-ethylcarbodiimide hydrochloride (0.401 g, 2.09 mmol) were sequentially added, and the reaction was stirred for two hours. The reaction was incomplete as determined by thin layer chromatography (TLC) analysis. The reaction was cooled to 4 °C, and 1-hydroxybenzotriazole (0.283 g, 2.09 mmol) was added. The reaction was allowed to warm to ambient temperature, stirred for 16 hours, and then diluted with chloroform (100 mL). The resulting solution was washed sequentially with water (100 mL), 4% aqueous sodium carbonate (2 x 100 mL), water (200 mL), and brine (150 mL); dried over sodium sulfate; filtered; and concentrated under reduced pressure. The residue was purified by HPFC followed by recrystallization from ethyl acetate to provide 0.68 g of 2-ethoxymethyl-7-(pyridin-3-yl)-1-{[1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-

yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white, crystalline solid, mp 191-192 °C.

Anal. Calcd for $C_{29}H_{34}N_6O_3 \cdot 0.3\ H_2O$: C, 66.98; H, 6.71; N, 16.16. Found: C, 66.87; H, 6.70; N, 15.77.

Example 183-186

Part A

7-Bromo-4-chloro-3-nitroquinoline (35.26 g, 123.8 mmol) was treated with 1-(3-aminopropyl)pyrrolidin-2-one (19.1 mL, 136.2 mmol) according to the method described in Part E of Example 1 to provide 40.87 g of 1-[3-(7-bromo-3-nitroquinolin-4-ylamino)propyl]pyrrolidin-2-one as a yellow solid.

Part B

1-[3-(7-Bromo3-nitroquinolin-4-ylamino)propyl]pyrrolidin-2-one was treated according to the methods described in Parts B, C, and D of Examples 152-156. 3-Methoxypropionyl chloride was used in Part C, and triethylamine (1.3 equivalents) was added to the reaction mixture. The crude product obtained in Part D was purified by flash chromatography on silica gel (eluting sequentially with 100:0 and 92.5:7.5 chloroform:methanol) followed by recrystallization from acetonitrile. The crystals were washed with acetonitrile and diethyl ether and dried in a vacuum oven at 60 °C to provide 1-{3-[7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one as a light grey solid.

Part C

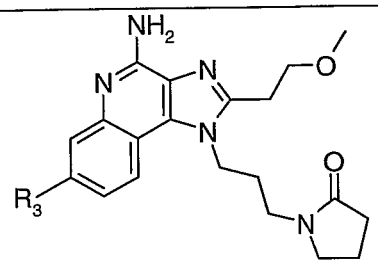
1-{3-[7-Bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The product from amination was recrystallized from isopropanol and then from ethanol. The crystals were washed with cold ethanol and diethyl ether and dried overnight in a vacuum oven at 60 °C to provide 1-{3-[4-amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one as a white solid, mp 228-231 °C.

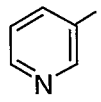
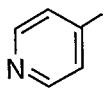
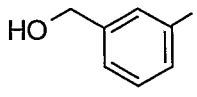
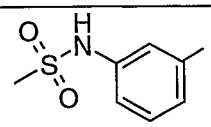
Anal. Calcd for $C_{20}H_{24}N_5O_2Br$: C, 53.82; H, 5.42; N, 15.69. Found: C, 53.48; H, 5.37; N, 15.45.

Part D

1-{3-[4-Amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one and the boronic acid or ester from the table below were coupled according to the method described in Examples 118-121. The work-up procedure described in Part F of Examples 125-135 was followed. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:00 to 70:30) followed by recrystallization from the solvent listed in the table below to provide the product shown in the table.

Examples 183-186



Example	Boronic acid or ester	Recrystallization solvent	R_3
183	3-Pyridine boronic acid	Ethanol	
184	Pyridine-4-boronic acid pinacol ester	Acetonitrile	
185	3-(Hydroxymethyl)phenylboronic acid	Ethanol	
186	[3-(Methylsulfonyl)aminophenyl]boronic acid	Not used	

Examples 183-186

Example	Name	Form	Mp (C°)	Anal.
183	1-{3-[4-Amino-2-(2-methoxyethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one	White solid	218-221	Calcd for $C_{25}H_{28}N_6O_2$: C, 67.55; H, 6.35; N, 18.91. Found: C, 67.30; H, 6.37; N, 18.79.
184	1-{3-[4-Amino-2-(2-methoxyethyl)-7-(pyridin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one	Off-white solid	232-235	Calcd for $C_{25}H_{28}N_6O_2$: C, 67.55; H, 6.35; N, 18.91. Found: C, 67.18; H, 6.49; N, 18.77.
185	1-{3-[4-Amino-7-(3-hydroxymethylphenyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one	Off-white needles	184-187	Calcd for $C_{27}H_{31}N_5O_3 \cdot 1.2\ H_2O$: C, 65.49; H, 6.80; N, 14.14. Found: C, 65.46; H, 6.82; N, 14.14.
186	*N*-(3-{4-Amino-2-(2-methoxyethyl)-1-[3-(2-oxopyrrolidin-1-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-7-yl}phenyl)methanesulfonamide	White powder	210-213	Calcd for $C_{27}H_{32}N_6O_4S$: C, 60.43; H, 6.01; N, 15.66. Found: C, 60.17; H, 6.15; N, 15.66.

Examples 187-190

Part A

6-Bromo-4-chloro-3-nitroquinoline (50.62 g, 177.8 mmol), prepared from 4-bromoaniline according to the methods described in Parts A-D of Example 1, was treated with 1-(3-aminopropyl)pyrrolidin-2-one (27.5 mL, 196 mmol) according to the method described in Part E of Example 1 to provide 61.41 g of 1-[3-(6-bromo-3-nitroquinolin-4-ylamino)propyl]pyrrolidin-2-one as a solid.

Part B

1-[3-(6-Bromo3-nitroquinolin-4-ylamino)propyl]pyrrolidin-2-one was treated according to the methods described in Parts B, C, and D of Examples 152-156. 3-Methoxypropionyl chloride was used in Part C. The crude product obtained in Part D was recrystallized from acetonitrile. The crystals were washed with cold acetonitrile and diethyl ether and dried in a vacuum oven at 60 °C to provide 1-{3-[8-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one as a light grey solid.

Part C

1-{3-[8-Bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The product from amination was recrystallized twice from isopropanol. The crystals were washed with cold isopropanol and dried in a vacuum oven at 60 °C to provide 1-{3-[4-amino-8-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one as a white solid, mp 185-188 °C.

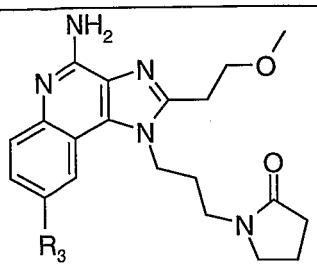
Anal. Calcd for $C_{20}H_{24}N_5O_2Br$: C, 53.82; H, 5.42; N, 15.69. Found: C, 53.67; H, 5.28; N, 15.45.

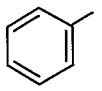
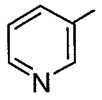
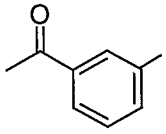
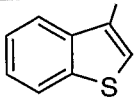
Part D

1-{3-[4-Amino-8-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one and the boronic acid or ester from the table below were coupled according to the method described in Examples 118-121. The reaction was heated at reflux overnight. The work-up procedure described in Part F of Examples 125-135 was followed. For Examples 1-3, the crude product

was recrystallized from the solvent indicated in the table below. For Example 4, the crude product was purified by HPFC™ (eluting with chloroform:CMA in a gradient from 100:00 to 75:25) followed by recrystallization from the solvents listed in the table below to provide the product shown in the table.

Examples 187-190



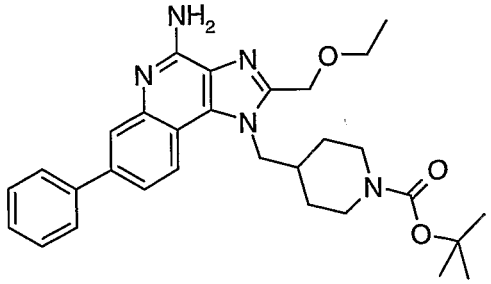
Example	Boronic acid or ester	Recrystallization solvent	R_3
187	Phenylboronic acid	Isopropanol	
188	3-Pyridine boronic acid	Ethanol (twice)	
189	3-Acetylphenyl boronic acid	Acetonitrile	
190	Thianaphthene-3-boronic acid	Propyl acetate then toluene	

Examples 187-190

Example	Name	Form	Mp (°C)	Anal.
187	1-{3-[4-Amino-2-(2-methoxyethyl)-8-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one	Off-white solid	207-210	Calcd for $C_{26}H_{29}N_5O_2 \bullet 0.2H_2O$: C, 69.85; H, 6.63; N, 15.67. Found: C, 69.51; H, 7.00; N, 15.42.
188	1-{3-[4-Amino-2-(2-methoxyethyl)-8-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one	Yellow solid	221-224	Calcd for $C_{25}H_{28}N_6O_2$: C, 67.55; H, 6.35; N, 18.91. Found: C, 67.30; H, 5.99; N, 18.91.
189	1-{3-[8-(3-Acetylphenyl)-4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one	Yellow solid	164-167	Calcd for $C_{28}H_{31}N_5O_3 \bullet 0.3H_2O$: C, 68.50; H, 6.49; N, 14.27. Found: C, 68.16; H, 6.43; N, 14.37.
190	1-{3-[4-amino-8-(benzo[b]thiophen-3-yl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one	White solid	202-205	Calcd for $C_{28}H_{29}N_5O_2S$: C, 67.31; H, 5.85; N, 14.02. Found: C, 67.07; H, 5.66; N, 13.88.

Example 191

tert-Butyl 4-[(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate



Part A

4-Chloro-3-nitro-7-phenylquinoline (8.35 g, 29.3 mmol) was treated with 1-(*tert*-butoxycarbonyl)-4-(aminomethyl)piperidine (7.54 g, 35.2 mmol) according to the method described in Part A of Examples 152-156. The crude solid was triturated with water, isolated by filtration, sonicated with diethyl ether, isolated by filtration, and dried for four hours in a vacuum oven at 40 °C to provide 12.78 g of *tert*-butyl 4-[(3-nitro-7-phenylquinolin-4-ylamino)methyl]piperidine-1-carboxylate as a yellow solid, mp 153-154 °C.

Part B

tert-Butyl 4-[(3-nitro-7-phenylquinolin-4-ylamino)methyl]piperidine-1-carboxylate was treated according to the methods described in Parts B-D of Example 152-156. In Part B, 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide was used instead of 1,1'-diethyl-4,4'-bipyridinium dibromide. Triethylamine (1.1 equivalents) was added to the reaction in Part C. The crude product from Part D was purified by flash column chromatography on silica gel (eluting with 95:5 chloroform:CMA) followed by recrystallization from dichloromethane:diethyl ether to provide *tert*-butyl 4-[(2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate as a white powder, mp 166-167 °C.

Anal. Calcd for $C_{30}H_{36}N_4O_3$: C, 71.97; H, 7.25; N, 11.19. Found: C, 71.86; H, 7.20; N, 11.11.

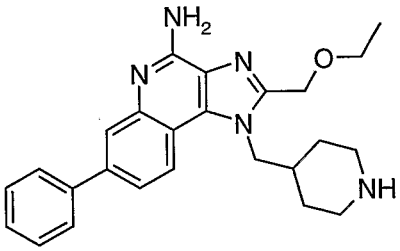
Part C

tert-Butyl 4-[(2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized. The product from amination was purified by column chromatography on silica gel (eluting with 90:10 chloroform:CMA) followed by recrystallization from ethyl acetate to provide *tert*-butyl 4-[(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate as a white powder, mp 194-195 °C.

Anal. Calcd for $C_{30}H_{37}N_5O_3$: C, 69.88; H, 7.23; N, 13.58. Found: C, 69.85; H, 7.16; N, 13.43.

Example 192

2-Ethoxymethyl-7-phenyl-1-(piperidin-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



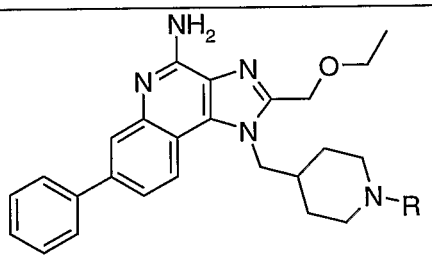
tert-Butyl 4-[(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate (0.64 g)was deprotected according to the method described in Example 177. The crude solid was dissolved in water (10 mL), and ammonium hydroxide was added until the solution was basic. The mixture was then extracted with chloroform (2 x 10 mL), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was recrystallized from acetonitrile and dried for 16 hours in a vacuum oven at 60 °C to provide 0.28 g of 2-ethoxymethyl-7-phenyl-1-(piperidin-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white, crystalline solid, mp 142-143 °C.

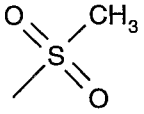
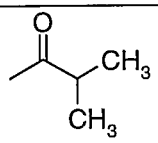
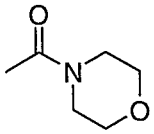
Anal. Calcd for $C_{25}H_{29}N_5O \cdot 0.5\ H_2O$: C, 70.73; H, 7.12; N, 16.50. Found: C, 70.58; H, 7.24; N, 16.61.

Examples 193-195

2-Ethoxymethyl-7-phenyl-1-(piperidin-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride was prepared according to the method described in Example 177. A solution of 2-ethoxymethyl-7-phenyl-1-(piperidin-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride (1.0 g, 2.05 mmol) and triethylamine (1.14 mL, 8.20 mmol) in dichloromethane (35 mL) was cooled to 4 °C. The reagent from the table below (2.05 mmol) was added dropwise, and the reaction was allowed to warm to ambient temperature and stirred for between one and three hours. The reaction mixture was diluted with chloroform, and the resulting solution was washed sequentially with water, 4% aqueous sodium carbonate (2 x), water, and brine and then concentrated under reduced pressure. The crude product was recystallized from the solvent listed in the table below to provide the compound shown in the table.

Example 193-195



Example	Reagent	Recrystallization solvent	R
193	Methanesulfonyl chloride	Ethyl acetate	
194	Isobutyryl chloride	Ethyl acetate then acetonitrile	
195	4-Morpholinecarbonyl chloride	Ethyl acetate	

Examples 193-195

Example	Name	Form	Mp (C°)	Anal.
193	2-Ethoxymethyl-1-{[1-(methanesulfonyl)piperidin-4-yl]methyl}-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	224-225	Calcd for $C_{26}H_{31}N_5O_3S$: C, 63.26; H, 6.33; N, 14.19. Found: C, 62.99; H, 6.49; N, 14.05.
194	2-Ethoxymethyl-1-[(1-isobutyrylpiperidin-4-yl)methyl]-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White, crystalline solid	156-158	Calcd for $C_{29}H_{35}N_5O_2 \cdot 0.5\ H_2O$: C, 70.42; H, 7.34; N, 14.16. Found: C, 70.17; H, 7.49; N, 14.13.
195	2-Ethoxymethyl-1-{[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]methyl}-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	208-209	Calcd for $C_{30}H_{36}N_6O_3$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.82; H, 6.99; N, 15.71.

Examples 196-198

Part A

4-Chloro-3-nitro-7-phenylquinoline (6.0 g, 21 mmol) was treated with 2-phenoxyethylamine (3.18 g, 23.2 mmol) according to the method described in Part A of Examples 125-135. The crude solid was triturated with water (100 mL), isolated by filtration, sonicated with diethyl ether, isolated by filtration, and

dried for two hours in a vacuum oven at 40 °C to provide 8.12 g of (3-nitro-7-phenylquinolin-4-yl)-(2-phenoxyethyl)amine as a yellow solid.

Part B

A solution of (3-nitro-7-phenylquinolin-4-yl)-(2-phenoxyethyl)amine (7.25 g, 18.8 mmol) in methanol (150 mL) was added to a Parr vessel charged with 5% platinum on carbon (0.84 g), and the reaction was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) for three hours. The reaction mixture was filtered through a layer of CELITE filter aid, and the filtrate was concentrated under reduced pressure, dissolved in toluene (2 x 25 mL), and concentrated under reduced pressure to provide N^4-(2-phenoxyethyl)-7-phenylquinoline-3,4-diamine as a yellow semi-solid.

Part C

A modification of the method described in Part C of Examples 125-135 was followed. A 0.2 M solution of the material from Part B and triethylamine (1 equivalent) in dichloromethane was treated with the acid chloride (1 equivalent) indicated in the table below.

Part D

The material from Part C was cyclized according to the method described in Part D of Examples 152-156. The crude product was purified by flash chromatography on silica gel (eluting with 95:5 chloroform:CMA) followed by recrystallization from ethyl acetate or ethyl acetate:diethyl ether to provide the following products.

Example 196: 2-Cyclopropylmethyl-1-(2-phenoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinoline was obtained as a white powder, mp 175-176 °C. Anal. Calcd for $C_{28}H_{25}N_3O$: C, 80.16; H, 6.01; N, 10.02. Found: C, 79.87; H, 5.92; N, 9.85.

Example 197: 2-Ethoxymethyl-1-(2-phenoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinoline was obtained as a yellow, crystalline solid, mp 137-138 °C. Anal. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.60; H, 6.10; N, 9.66.

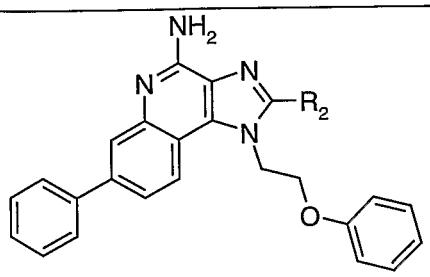
Example 198: 2-(4-Methoxybenzyl)-1-(2-phenoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinoline was obtained as a white, crystalline powder, mp 205-

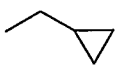
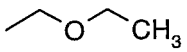
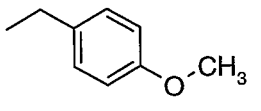
206 °C. Anal. Calcd for $C_{32}H_{27}N_3O_2$: C, 79.15; H, 5.60; N, 8.65. Found: C, 78.87; H, 5.65; N, 8.60.

Part E

The material from Part D was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized. The product from amination was purified by column chromatography on silica gel (eluting with 95:5 or 90:10 chloroform:CMA) followed by recrystallization from ethyl acetate to provide the products shown in the table below.

Examples 196-198



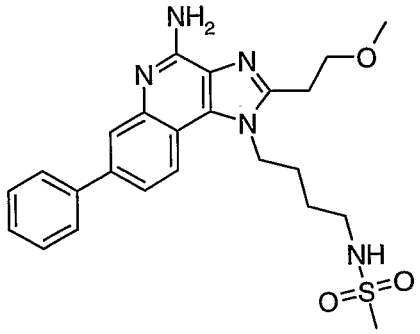
Example	Acid Chloride	R_2
196	Cyclopropylacetyl chloride	
197	Ethoxyacetyl chloride	
198	4-Methoxyphenylacetyl chloride	

Examples 196-198

Example	Name	Form	Mp (C°)	Anal.
196	2-Cyclopropylmethyl-1-(2-phenoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	188-189	Calcd for $C_{28}H_{26}N_4O$: C, 77.39; H, 6.03; N, 12.89. Found: C, 77.10; H, 6.03; N, 12.85.
197	2-Ethoxymethyl-1-(2-phenoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White, crystalline solid	159-160	Calcd for $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78. Found: C, 73.72; H, 5.94; N, 12.78.
198	2-(4-Methoxybenzyl)-1-(2-phenoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Fluffy, white powder	197-198	Calcd for $C_{32}H_{28}N_4O_2$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.55; H, 5.75; N, 11.12.

Example 199

N-{4-[4-Amino-2-(2-methoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide



Part A

Under a nitrogen atmosphere, a solution of *tert*-butyl *N*-(4-aminobutyl)carbamate (13.8 g, 73.4 mmol) and triethylamine (15.3 mL, 110 mmol) was cooled to 0 °C. Methanesulfonyl chloride (6.3 mL, 81 mmol) was added, and the reaction was allowed to warm to ambient temperature and stirred overnight. Aqueous acetic acid (200 mL of 10%) was added. The organic layer was then separated and washed with water (200 mL), saturated aqueous sodium bicarbonate (200 mL), water (200 mL), and brine; dried over sodium sulfate; filtered; and concentrated under reduced pressure to provide 18.9 g of *tert*-butyl [4-(methanesulfonylamino)butyl]carbamate as an off-white solid.

Part B

A solution of hydrochloric acid in ethanol was added to a solution of *tert*-butyl [4-(methanesulfonylamino)butyl]carbamate (18.9 g, 71.1 mmol) in ethanol (100 mL), and the reaction was heated at 100 °C for two hours. The solvent was removed under reduced pressure. A mixture of dichloromethane:hexanes was added to the resulting oil and removed under reduced pressure; this process was repeated several times. The residue was dried for three days under vacuum to provide 14.3 g of *N*-(4-aminobutyl)methanesulfonamide hydrochloride as a tan solid.

Part C

N-(4-aminobutyl)methanesulfonamide hydrochloride (7.8 g, 39 mmol) was added to a suspension of 4-chloro-3-nitro-7-phenylquinoline (35 mmol) and

triethylamine (8.0 g, 79 mmol) in NMP (80 mL), and the reaction was stirred at ambient temperature overnight. The resulting solution was poured into water (350 mL) to form a solid, which was isolated by filtration, washed with water, air-dried, and recrystallized from acetonitrile to provide 12.0 g of *N*-[4-(3-nitro-7-phenylquinolin-4-ylamino)butyl]methanesulfonamide as yellow plates.

Part D

The method described in Part B of Examples 125-135 was used to convert *N*-[4-(3-nitro-7-phenylquinolin-4-ylamino)butyl]methanesulfonamide (12.0 g, 29.0 mmol) to *N*-[4-(3-amino-7-phenylquinolin-4-ylamino)butyl]methanesulfonamide, which was isolated as a brown solid.

Part E

The material from Part D was treated according to the method described in Part A of Example 9. The crude product was recrystallized from methyl ethyl ketone and then purified twice by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 75:25 and eluting with acetone:methanol in a gradient from 100:0 to 95:5).

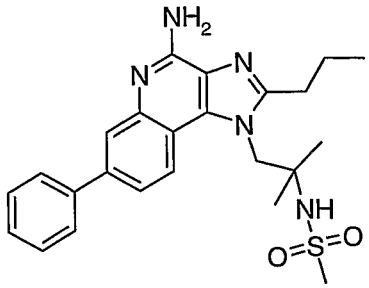
Part F

N-{4-[2-(2-methoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide was oxidized and then aminated according to the methods described in Parts H and I of Example 1. Both reactions were carried out in chloroform. The oxidation product was recrystallized from 5:1 acetonitrile:ethyl acetate and dried under vacuum overnight at 45 °C. The amination product was recrystallized from acetonitrile and dried in a vacuum oven at 70 °C to provide *N*-{4-[4-amino-2-(2-methoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide as a white solid, mp 201-202 °C.

Anal. Calcd for $C_{24}H_{29}N_5O_3S$: C, 61.65; H, 6.25; N, 14.98. Found: C, 61.55; H, 6.11; N, 15.01.

Example 200

N-[2-(4-Amino-7-phenyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide



Part A

A solution of 1,2-diamino-2-methylpropane (9.3 mL, 88.9 mmol) and triethylamine (5.0 mL, 35.5 mmol) in dichloromethane (100 mL) was cooled to 0 °C. A solution of 4-chloro-3-nitro-7-phenylquinoline (5.06 g, 17.8 mmol) in dichloromethane (50 mL) was added over a period of 45 minutes, and then the reaction was allowed to warm to ambient temperature. The solution was washed sequentially with water (2 x 100 mL) and brine (150 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide N^1-(3-nitro-7-phenylquinolin-4-yl)-2-methylpropane-1,2-diamine as an orange solid.

Part B

A solution of N^1-(3-nitro-7-phenylquinolin-4-yl)-2-methylpropane-1,2-diamine (5.85 g, 17.4 mmol) in dichloromethane (200 mL) was cooled to 0 °C. Triethylamine (3.6 mL, 26 mmol) and methanesulfonic anhydride (3.03, 17.4 mmol) were sequentially added. The reaction was allowed to warm to ambient temperature and stirred for two hours. Additional methanesulfonic anhydride (0.76 g, 4.4 mmol) was added, and the reaction was stirred overnight. A precipitate was present and was isolated by filtration, washed with water, and dried for two hours under high vacuum at 75 °C. The filtrate was washed sequentially with water (2 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and recrystallized from dichloroethane. The two solids were combined to provide 5.26 g of *N*-[1,1-dimethyl-2-(3-nitro-7-phenylquinolin-4-ylamino)ethyl]methanesulfonamide as a yellow powder.

Part C

The method described in Part B of Examples 125-135 was used to convert *N*-[1,1-dimethyl-2-(3-nitro-7-phenylquinolin-4-ylamino)ethyl]methanesulfonamide (5.26 g, 12.6 mmol) to 4.53 g of *N*-[2-(3-amino-7-phenylquinolin-4-ylamino)-1,1-dimethylethyl]methanesulfonamide, which was isolated as a yellow-orange solid.

Part D

N-[2-(3-Amino-7-phenylquinolin-4-ylamino)-1,1-dimethylethyl]methanesulfonamide (2.20 g, 5.04 mmol) was treated with trimethyl orthobutyrate (0.90 mL, 5.5 mmol) according to the method described in Part G of Example 1. The chromatographic purification was carried out eluting with 92.5:7.5 dichloromethane:methanol to provide 1.8 g of *N*-[2-(7-phenyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide as a tan solid.

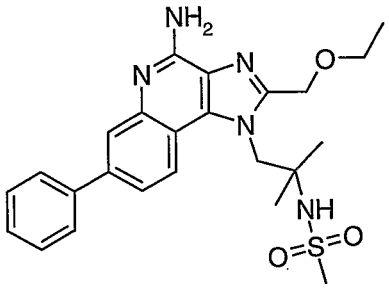
Part E

N-[2-(7-Phenyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation reaction was carried out in chloroform, and the product was not recrystallized. The product from amination was recrystallized from ethanol, and isolated by filtration. The solid was recrystallized from acetonitrile, and the crystals were dissolved in dichloromethane:methanol, concentrated under reduced pressure, and dried under high vacuum at 60 °C to provide *N*-[2-(4-amino-7-phenyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide as a white, crystalline solid, mp 135-141 °C.

Anal. Calcd for $C_{24}H_{29}N_5O_2S$: C, 63.83; H, 6.47; N, 15.51. Found: C, 63.48; H, 6.80; N, 15.34.

Example 201

N-[2-(4-Amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide



Part A

A modification of the method described in Part C of Examples 125-135 was used to treat *N*-[1,1-dimethyl-2-(3-amino-7-phenylquinolin-4-ylamino)ethyl]methanesulfonamide (2.33 g, 5.33 mmol) with ethoxyacetyl chloride (0.72 g, 5.87 mmol). Triethylamine (1.5 mL, 11 mmol) was added to the reaction, which was stirred overnight.

Part B

A solution of the material from Part A and triethylamine (1.5 mL, 11 mmol) in anhydrous toluene (100 mL) was heated at reflux overnight. The solvent was then removed under reduced pressure, and the residue was dissolved in dichloromethane (100 mL). The resulting solution was washed sequentially with 1% aqueous sodium carbonate (2 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) to provide 2.07 g of *N*-[2-(2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide as a yellow solid.

Part C

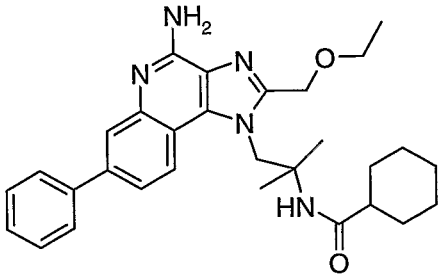
N-[2-(2-Ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide was oxidized and then aminated according to the methods described in Parts H and I or Example 1. The oxidation reaction was carried out in chloroform, and the product was not recrystallized. The product from amination was recrystallized from acetonitrile, and the crystals

were dissolved in dichloromethane:methanol, concentrated under reduced pressure, and dried in a vacuum oven to provide *N*-[2-(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide as a white powder, mp 239-242 °C.

Anal. Calcd for $C_{24}H_{29}N_5O_2S \bullet 0.3H_2O$: C, 60.94; H, 6.31; N, 14.81. Found: C, 60.91; H, 6.03; N, 14.71.

Example 202

Cyclohexane *N*-[2-(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]carboxamide



Part A

A solution of N^1-(3-nitro-7-phenylquinolin-4-yl)-2-methylpropane-1,2-diamine (3.56 g, 10.6 mmol) in dichloromethane (100 mL) was cooled to 0 °C. Triethylamine (3.0 mL, 21 mmol) and cyclohexanecarbonyl chloride (1.55 mL, 11.6 mmol) were sequentially added. The reaction was allowed to warm to ambient temperature and stirred for two hours. The reaction was washed sequentially with water (2 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 65:35 hexanes:ethyl acetate) to provide 3.33 g of cyclohexane *N*-[1,1-dimethyl-2-(3-nitro-7-phenylquinolin-4-ylamino)ethyl]carboxamide as a yellow solid.

Part B

The method described in Part B of Examples 125-135 was used to convert cyclohexane *N*-[1,1-dimethyl-2-(3-nitro-7-phenylquinolin-4-ylamino)ethyl]carboxamide (3.33 g, 7.46 mmol) to 3.06 g of cyclohexane *N*-[2-

(3-amino-7-phenylquinolin-4-ylamino)-1,1-dimethylethyl]carboxamide, which was isolated as an orange solid.

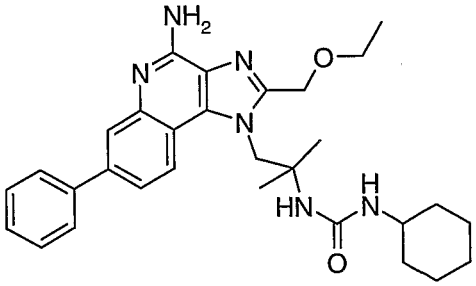
Part C

Cyclohexane *N*-[2-(3-amino-7-phenylquinolin-4-ylamino)-1,1-dimethylethyl]carboxamide was treated according to the methods described in Parts A-C Example 201. The product from amination was purified by column chromatography on silica gel (eluting with 92.5:7.5 dichloromethane:methanol) followed by recrystallization from isopropanol. The crystals were dissolved in dichloromethane:methanol, concentrated under reduced pressure, and dried for two days under high vacuum at 65 °C to provide cyclohexane *N*-[2-(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]carboxamide as a white powder, mp 195-198 °C.

Anal. Calcd for $C_{30}H_{37}N_5O_2 \bullet 0.25H_2O$: C, 71.47; H, 7.50; N, 13.89. Found: C, 71.49; H, 7.54; N, 13.88.

Example 203

N-[2-(4-Amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-*N'*-cyclohexylurea



Part A

A solution of N^1-(3-nitro-7-phenylquinolin-4-yl)-2-methylpropane-1,2-diamine (3.56 g, 10.6 mmol) in dichloromethane (100 mL) was cooled to 0 °C. Cyclohexyl isocyanate (3.00 mL, 23.5 mmol) was added over the course of a day, and the reaction was stirred at ambient temperature for three days. The solvent was removed under reduced pressure. Xylenes (3 cx 100 mL) were added and removed under reduced pressure to provide *N*-cyclohexyl-*N'*-[1,1-dimethyl-2-(3-nitro-7-phenylquinolin-4-ylamino)ethyl]urea as a yellow solid.

Part B

The method described in Part B of Examples 125-135 was used to convert *N*-cyclohexyl-*N'*-[1,1-dimethyl-2-(3-nitro-7-phenylquinolin-4-ylamino)ethyl]urea (4.88 g, 10.6 mmol) to 4.35 g of *N*-[2-(3-amino-7-phenylquinolin-4-ylamino)-1,1-dimethylethyl]-*N'*-cyclohexylurea, which was isolated as an orange powder.

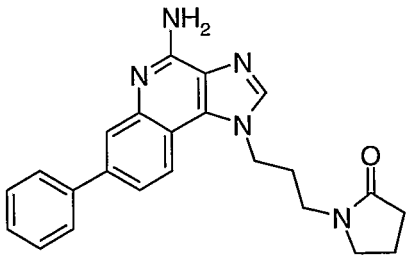
Part C

N-cyclohexyl-*N'*-[2-(3-amino-7-phenylquinolin-4-ylamino)-1,1-dimethylethyl]urea was treated according to the methods described in Parts A-C Example 201. The product from amination was recrystallized twice from ethanol. The crystals were dissolved in dichloromethane, and the resulting solution was washed sequentially with water (2 x) and brine, dried over sodium sulfate, filtered, concentrated under reduced pressure, and dried for two days under high vacuum at 65 °C to provide *N*-[2-(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-*N'*-cyclohexylurea as an off-white powder, mp 152-156 °C.

Anal. Calcd for $C_{30}H_{38}N_6O_2$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.78; H, 7.63; N, 16.24.

Examples 204

1-[3-(4-Amino-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]pyrrolidin-2-one



Part A

4-Chloro-3-nitro-7-phenylquinoline (3.51 g, 12.3 mmol) was treated with 1-(3-aminopropyl)pyrrolidin-2-one (2.3 mL, 16 mmol) according to the method described in Part E of Example 1 to provide 4.23 g of 1-[3-(3-nitro-7-phenylquinolin-4-ylamino)propyl]pyrrolidin-2-one as a yellow solid.

Part B

The method described in Part B of Examples 152-156 was used to convert 1-[3-(3-nitro-7-phenylquinolin-4-ylamino)propyl]pyrrolidin-2-one (4.25 g, 10.9 mmol) to 3.66 g of 1-[3-(3-amino-7-phenylquinolin-4-ylamino)propyl]pyrrolidin-2-one, which was obtained as a brown solid. In Part B, 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide was used instead of 1,1'-diethyl-4,4'-bipyridinium dibromide.

Part C

Triethyl orthoformate (2.50 mL, 15.0 mmol) was added to a solution of 1-[3-(3-amino-7-phenylquinolin-4-ylamino)propyl]pyrrolidin-2-one (3.59 g, 9.96 mmol) and pyridine hydrochloride (50 mg, 0.43 mmol) in anhydrous toluene (65 mL) and 1,2-dichloroethane (35 mL), and the reaction was heated at reflux overnight under a nitrogen atmosphere. The solution was then washed with saturated aqueous sodium carbonate (150 mL). The aqueous layer was extracted with dichloromethane (2 x 150 mL), and the combined organic fractions were washed with brine (150 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was dissolved in dichloromethane (5 mL), and diethyl ether (100 mL) was added to form a solid, which was isolated by filtration and dried in a vacuum oven at 60 °C to provide 2.51 g of a light brown solid. A portion of the product was recrystallized from 25:75 ethyl acetate:heptane and dried in a vacuum oven at 60 °C to provide 1-[3-(7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]pyrrolidin-2-one as a light brown solid, mp 138-141 °C.

Anal. Calcd. for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.45; H, 6.17; N, 15.06.

Part D

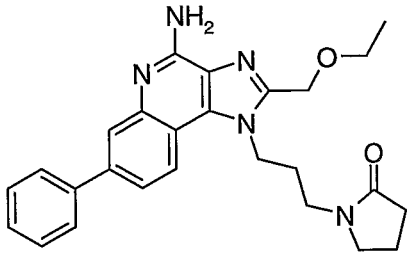
1-[3-(7-Phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]pyrrolidin-2-one was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The product from amination was purified twice by column chromatography on silica gel (eluting with chloroform:CMA in gradients from 100:0 to 70:30). The resulting solid was washed with diethyl ether, recrystallized from acetonitrile, and dried in a vacuum oven at 60 °C to provide

1-[3-(4-amino-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]pyrrolidin-2-one as a light brown solid, mp 201-204 °C.

Anal. Calcd. for $C_{23}H_{23}N_5O$: C, 71.67; H, 6.01; N, 18.17. Found: C, 71.64; H, 5.95; N, 18.48.

Example 205

1-[3-(4-Amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]pyrrolidin-2-one



Part A

1-[3-(3-Amino-7-phenylquinolin-4-ylamino)propyl]pyrrolidin-2-one (2.21 g, 6.13 mmol) was treated with ethoxyacetyl chloride (0.95 mL, 8.76 mmol) according to the methods described in Parts C and D of Examples 152-156. Triethylamine (8.6 mmol) was added in Part C. The product from Part D was purified by column chromatography on silica gel (eluting with acetone and then chloroform:methanol in a gradient from 95:5 to 90:10) to provide 1.49 g of 1-[3-(2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]pyrrolidin-2-one as a brown solid.

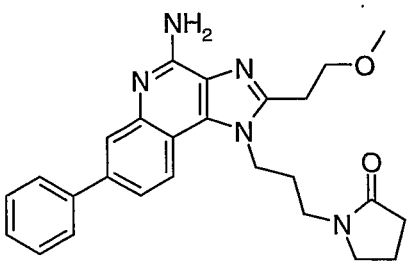
Part B

1-[3-(2-Ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]pyrrolidin-2-one was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The product from amination was purified by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 100:0 to 75:25) followed by recrystallization from acetonitrile and drying in a vacuum oven at 60 °C to provide 1-[3-(4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]pyrrolidin-2-one as a light brown solid, mp 199-203 °C.

Anal. Calcd. for $C_{26}H_{29}N_5O_2$: C, 70.41; H, 6.59; N, 15.79. Found: C, 70.04; H, 6.55; N, 15.55.

Example 206

1-{3-[4-Amino-2-(2-methoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one



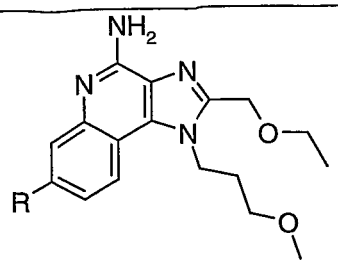
The methods described in Parts A of Example 204 were used to treat 1-[3-(3-amino-7-phenylquinolin-4-ylamino)propyl]pyrrolidin-2-one (1.19 g, 3.30 mmol) with 3-methoxypropionyl chloride (0.45 mL, 4.1 mmol) to afford 1-{3-[2-(2-methoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one, which was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The product from amination was recrystallized twice from acetonitrile and dried in a vacuum oven at 60 °C to provide 1-{3-[4-amino-2-(2-methoxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one as a light brown solid, mp 187-191 °C.

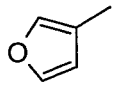
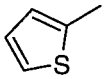
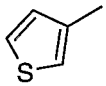
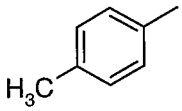
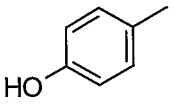
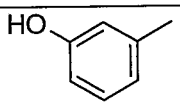
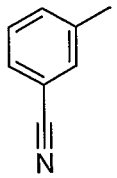
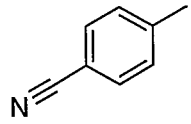
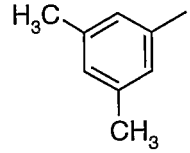
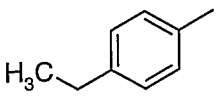
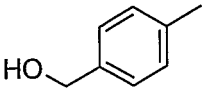
Anal. Calcd. for $C_{26}H_{29}N_5O_2 \bullet 0.13H_2O$: C, 70.05; H, 6.61; N, 15.71. Found: C, 69.66; H, 6.73; N, 15.82.

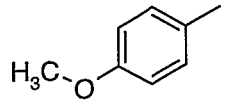
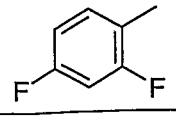
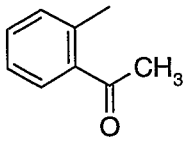
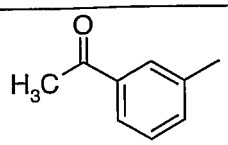
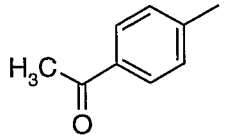
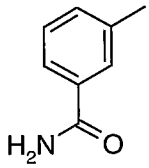
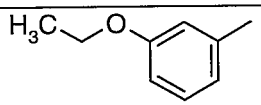
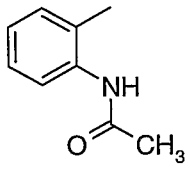
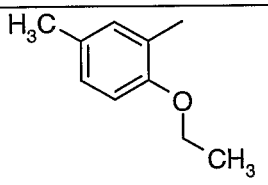
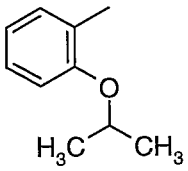
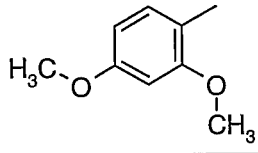
Examples 207-243

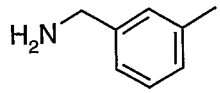
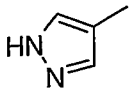
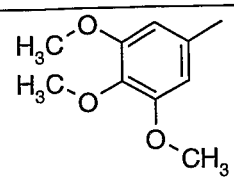
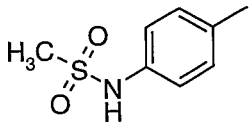
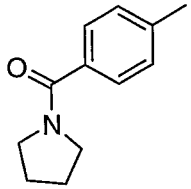
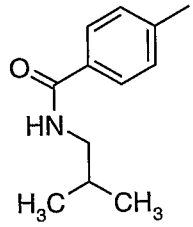
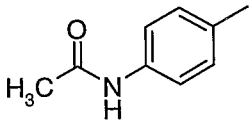
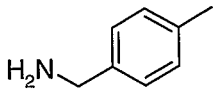
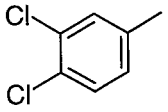
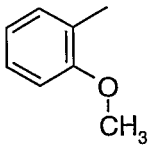
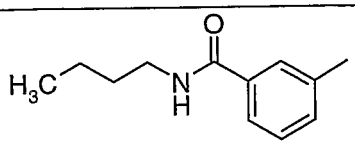
7-Bromo-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65 and then purified by prep HPLC according to procedures described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

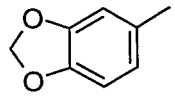
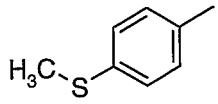
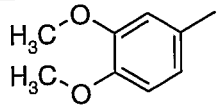
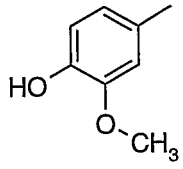
Examples 207-243



Example	R	Measured Mass (M+H)
207		381.1920
208		397.1703
209		397.1696
210		405.2279
211		407.2063
212		407.2091
213		416.2078
214		416.2076
215		419.2453
216		419.2456
217		421.2240

218		421.2233
219		427.1955
220		433.2238
221		433.2244
222		433.2226
223		434.2203
224		435.2425
225		448.2346
226		449.2544
227		449.2560
228		451.2355

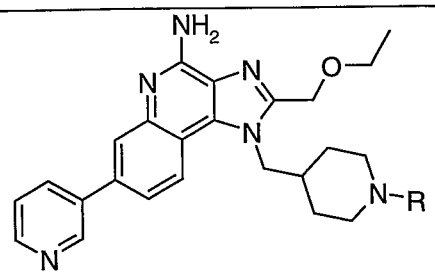
229		420.2405
230		381.2043
231		481.2441
232		484.1996
233		488.2650
234		490.2800
235		448.2330
236		420.2382
237		459.1323
238		421.2232
239		490.2826

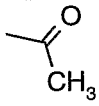
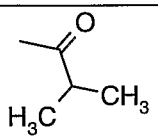
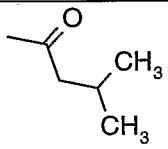
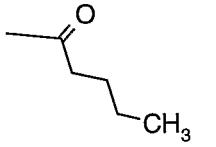
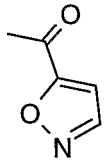
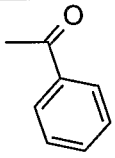
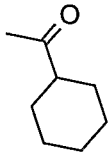
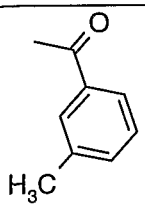
240		435.2045
241		437.2012
242		451.2355
243		437.2174

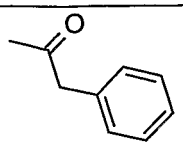
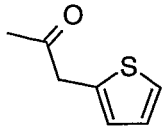
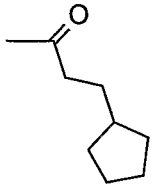
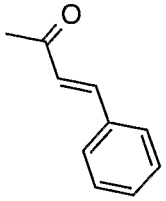
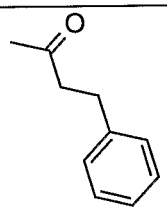
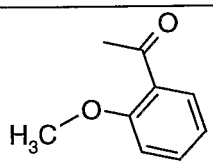
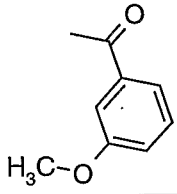
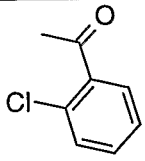
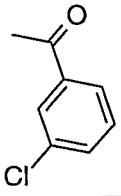
Examples 244-323

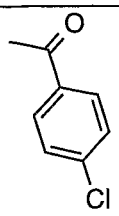
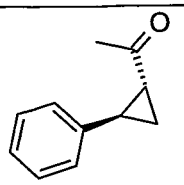
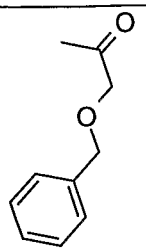
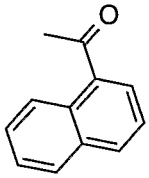
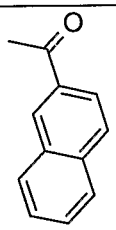
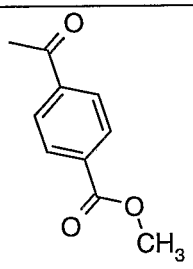
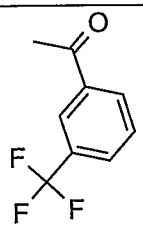
A reagent from the table below, (0.064 mmol, 1.1 equivalents) was added to a test tube containing a solution of 2-ethoxymethyl-1-(piperidin-4-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride (30 mg, 0.057 mmol) and *N,N*-diisopropylethylamine (0.048 mL, 0.27 mmol, 4.8 equivalents) in chloroform (2 mL). The test tube was capped placed on a shaker at ambient temperature overnight. One drop of deionized water was then added to each test tube, and the solvent was removed by vacuum centrifugation. For Example 323, the capped test tube was heated at 60 °C overnight in a sand bath, and then lithium trifluoromethanesulfonimide (3 mg) was added followed by shaking for an additional four hours. The products were purified by prep HPLC according to the methods described above. 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.

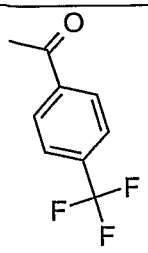
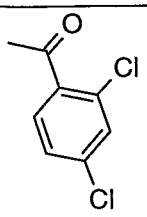
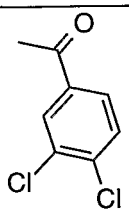
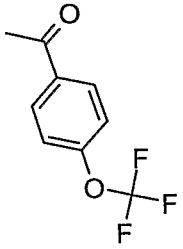
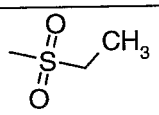
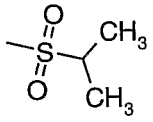
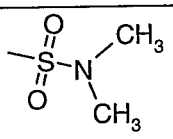
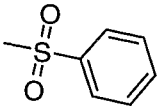
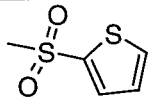
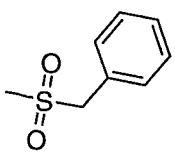
Examples 244-323

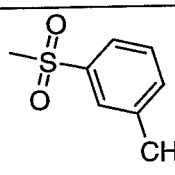
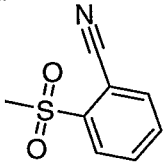
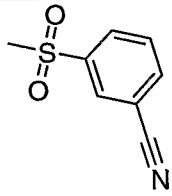
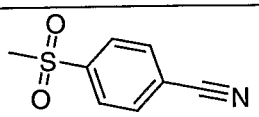
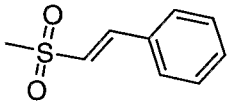
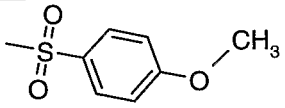
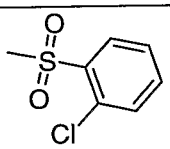
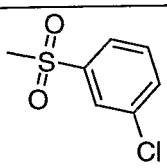
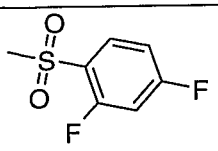
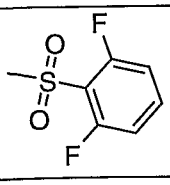
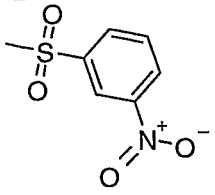


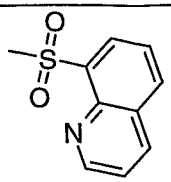
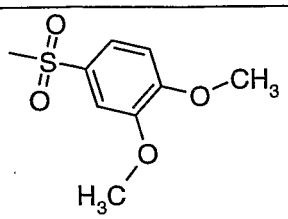
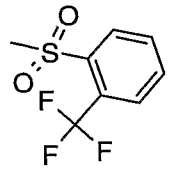
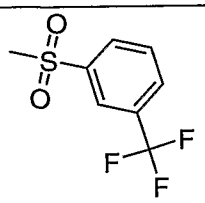
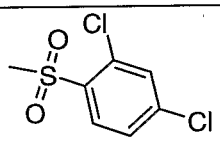
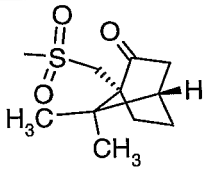
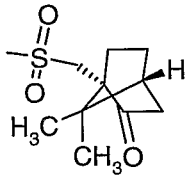
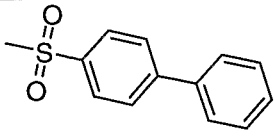
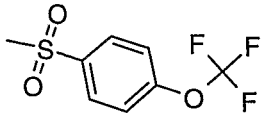
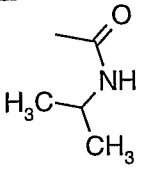
Example	Reagent	R	Measured Mass (M+H)
244	Acetyl chloride		459.2510
250	Isobutyryl chloride		487.2840
245	Isovaleryl chloride		501.2990
246	Pentanoyl chloride		501.2957
247	Isoxazole-5-carbonyl chloride		512.2435
248	Benzoyl chloride		521.2667
249	Cyclohexanecarbonyl chloride		527.3166
250	*m*-Toluoyl chloride		535.2848

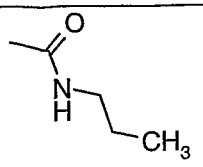
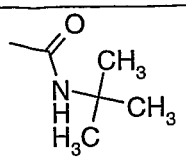
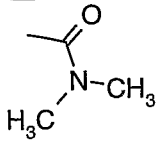
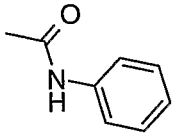
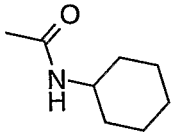
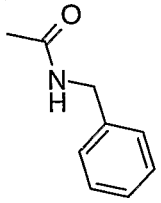
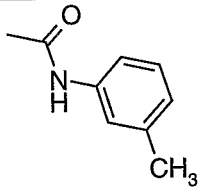
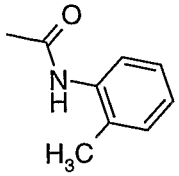
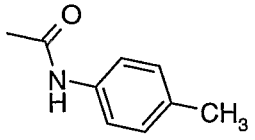
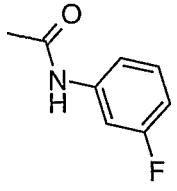
251	Phenylacetyl chloride		535.2853
252	Thiophene-2-acetyl chloride		541.2407
253	3-Cyclopentylpropionyl chloride		541.3304
254	Cinnamoyl chloride		547.2837
255	Hydrocinnamoyl chloride		549.3021
256	2-Methoxybenzoyl chloride		551.2809
257	*m*-Anisoyl chloride		551.2786
258	2-Chlorobenzoyl chloride		555.2264
259	3-Chlorobenzoyl chloride		555.2272

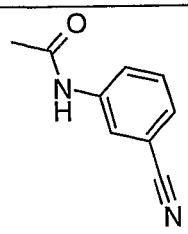
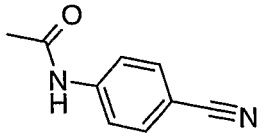
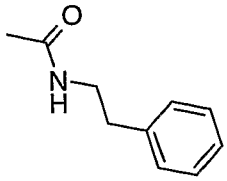
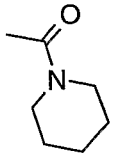
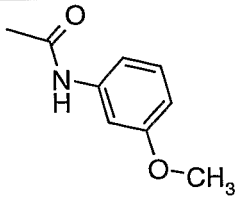
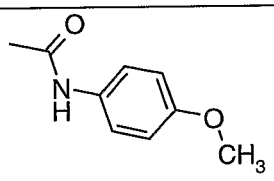
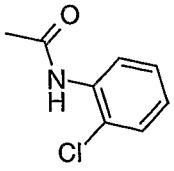
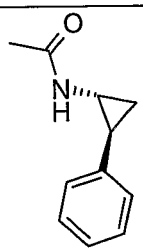
260	4-Chlorobenzoyl chloride		555.2281
261	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		561.2970
262	Benzyloxyacetyl chloride		565.2938
263	1-Naphthoyl chloride		571.2817
264	2-Naphthoyl chloride		571.2817
265	Methyl 4-chlorocarbonylbenzoate		579.2716
266	3-(Trifluoromethyl)benzoyl chloride		589.2557

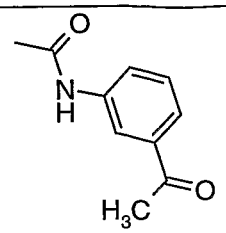
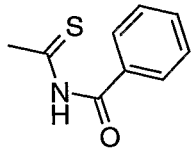
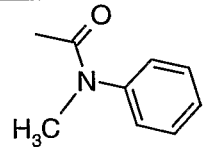
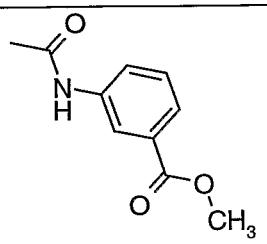
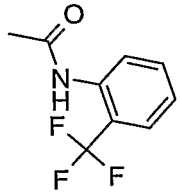
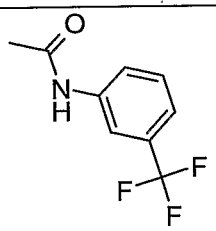
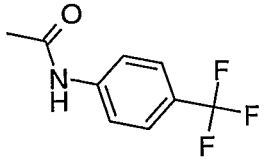
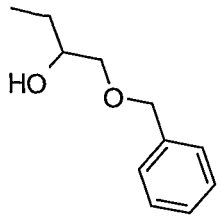
267	4-(Trifluoromethyl)benzoyl chloride		589.2585
268	2,4-Dichlorobenzoyl chloride		589.1870
269	3,4-Dichlorobenzoyl chloride		589.1912
270	4-(Trifluoromethoxy)benzoyl chloride		605.2531
271	Ethanesulfonyl chloride		509.2364
272	Isopropylsulfonyl chloride		523.2523
273	Dimethylsulfamoyl chloride		524.2463
274	Benzenesulfonyl chloride		557.2380
275	2-Thiophenesulfonyl chloride		563.1921
276	α-Toluenesulfonyl chloride		571.2524

277	*m*-Toluenesulfonyl chloride		571.2509
278	2-Cyanobenzenesulfonyl chloride		582.2325
279	3-Cyanobenzenesulfonyl chloride		582.2301
280	4-Cyanobenzenesulfonyl chloride		582.2322
281	*trans*-β-Styrenesulfonyl chloride		583.2543
282	4-Methoxybenzenesulfonyl chloride		587.2435
283	2-Chlorobenzenesulfonyl chloride		591.1967
284	3-Chlorobenzenesulfonyl chloride		591.1970
285	2,4-Difluorobenzenesulfonyl chloride		593.2180
286	2,6-Difluorobenzenesulfonyl chloride		593.2167
287	3-Nitrobenzenesulfonyl chloride		602.2214

288	8-Quinolinesulfonyl chloride		608.2483
289	3,4-Dimethoxybenzenesulfonyl chloride		617.2534
290	2-(Trifluoromethyl)benzenesulfonyl chloride		625.2228
291	3-(Trifluoromethyl)benzenesulfonyl chloride		625.2214
292	2,4-Dichlorobenzenesulfonyl chloride		625.1567
293	(1*R*)-(-)-10-Camphorsulfonyl chloride		631.3110
294	(1*S*)-(-)-10-Camphorsulfonyl chloride		631.3090
295	4-Biphenylsulfonyl chloride		633.2662
296	4-(Trifluoromethoxy)benzenesulfonyl chloride		641.2178
297	Isopropyl isocyanate		502.2964

298	*n*-Propyl isocyanate		502.2924
299	*tert*-Butyl isocyanate		516.3080
300	Dimethylcarbamyl chloride		488.2809
301	Phenyl isocyanate		536.2817
302	Cyclohexyl isocyanate		542.3281
303	Benzyl isocyanate		550.2914
304	*m*-Tolyl isocyanate		550.2971
305	*o*-Tolyl isocyanate		550.2964
306	*p*-Tolyl isocyanate		550.2953
307	3-Fluorophenyl isocyanate		554.2717

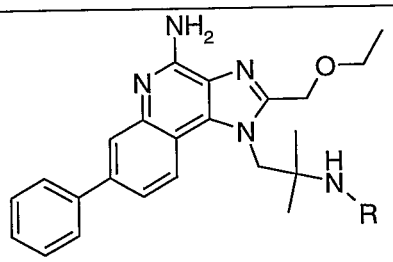
308	3-Cyanophenyl isocyanate		561.2725
309	4-Cyanophenyl isocyanate		561.2756
310	Phenethyl isocyanate		564.3129
311	1-Piperidinecarbonyl chloride		528.3115
312	3-Methoxyphenyl isocyanate		566.2924
313	4-Methoxyphenyl isocyanate		566.2906
314	2-Chlorophenyl isocyanate		570.2419
315	*trans*-2-Phenylcyclopropyl isocyanate		576.3120

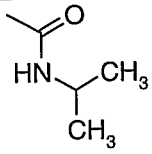
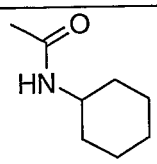
316	3-Acetylphenyl isocyanate		578.2910
317	Benzoyl Isothiocyanate		580.2478
318	*N*-Methyl-*N*-phenylcarbamoyl chloride		550.2927
319	Methyl 3-Isocyanatobenzoate		594.2820
320	2-(Trifluoromethyl)phenyl isocyante		604.2616
321	3-(Trifluoromethyl)phenyl isocyante		604.2638
322	4-(Trifluoromethyl)phenyl isocyante		604.2658
323	Benzyl glycidyl ether		581.3278

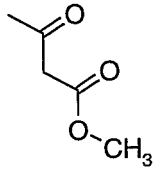
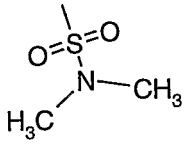
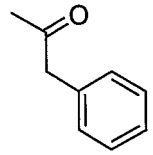
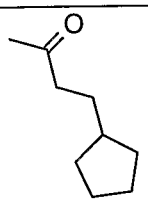
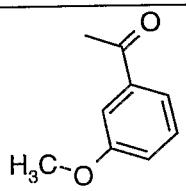
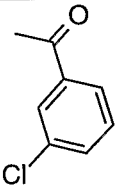
Examples 323-331

1-(2-Amino-2-methylpropyl)-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine was prepared from N^1-(3-nitro-7-phenylquinolin-4-yl)-2-methylpropane-1,2-diamine according to the methods described in Part C of Example 200 and Parts A-C of Example 201. A reagent from the table below, (0.051-0.058 mmol, 1.1 equivalents) was added to a test tube containing a solution of 1-(2-amino-2-methylpropyl)-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (20 mg, 0.051 mmol) and *N,N*-diisopropylethylamine (0.018 mL, 0.10 mmol, 2 equivalents) in chloroform (2 mL). The test tube was capped placed on a shaker at ambient temperature overnight. For Examples 324 and 327, the test tubes were then heated on a sand bath for two hours at 50 °C. Ammonium hydroxide (2 drops) was added to the other reactions, and they were placed back on the shaker. The solvent was removed by vacuum centrifugation, and the products were purified by prep HPLC according to the methods described above. 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.

Examples 324-331



Example	Reagent	R	Measured Mass (M+H)
324	Dimethylcarbamyl chloride		475.2825
325	Cyclohexyl isocyanate		515.3126

326	Methyl malonyl chloride		490.2459
327	Dimethylsulfamoyl chloride		497.2338
328	Phenylacetyl chloride		508.2685
329	3-Cyclopentylpropionyl chloride		514.3140
330	*m*-Anisolyl chloride		524.2621
331	3-Chlorobenzoyl chloride		528.2164

Examples 332-362

Part A

tert-Butyl 4-[(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate (11.83 g, 22.82 mmol) was treated according to the method described in Example 177 to provide 9.73 g of 7-bromo-2-ethoxymethyl-1-(piperidin-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride as a white, crystalline solid, mp > 300 °C.

Part B

The method described in Examples 178-181 was used to treat 7-bromo-2-ethoxymethyl-1-(piperidin-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

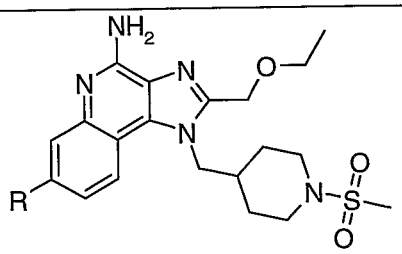
dihydrochloride (4.95 g, 10.1 mmol) with methanesulfonic anhydride (1.76 g, 10.1 mmol). The reaction was carried out in dichloromethane (150 mL). Following chromatographic purification (eluting with chloroform:CMA in a gradient from 100:0 to 90:10), the product was recrystallized from ethyl acetate to provide 2.37 g of 7-bromo-2-ethoxymethyl-1-{[1-(methanesulfonyl)piperidin-4-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white, crystalline solid, mp 233-234 °C.

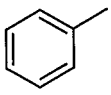
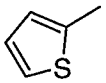
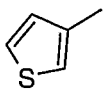
Anal. Calcd for $C_{20}H_{26}BrN_5O_3S$: C, 47.87; H, 5.34; N, 13.96. Found: C, 48.14; H, 5.28; N, 13.56.

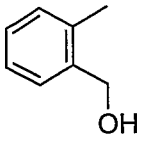
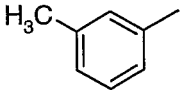
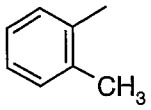
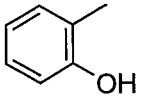
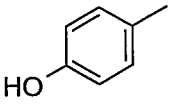
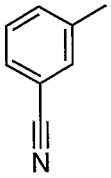
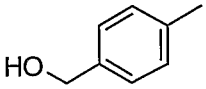
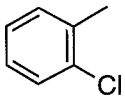
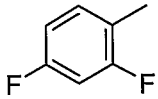
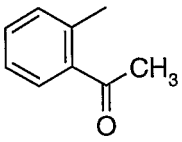
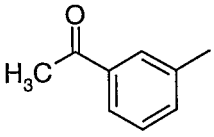
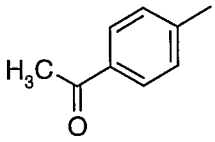
Part C

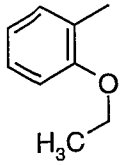
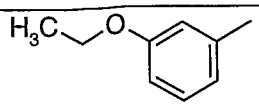
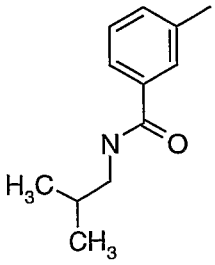
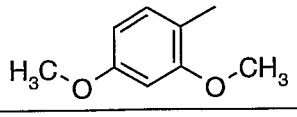
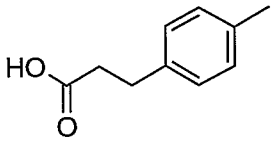
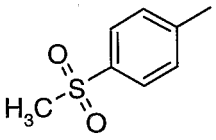
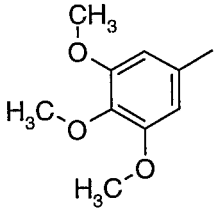
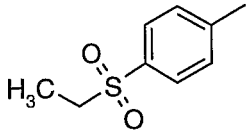
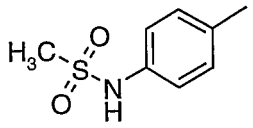
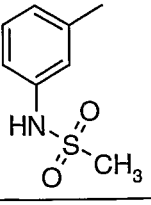
7-Bromo-2-ethoxymethyl-1-{[1-(methanesulfonyl)piperidin-4-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The preoducts were purifed by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

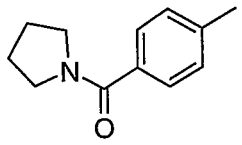
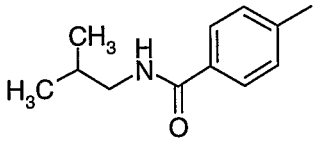
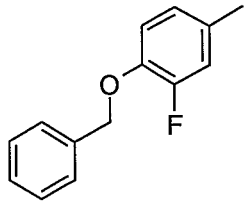
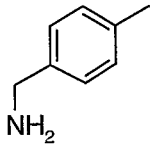
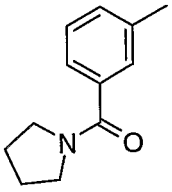
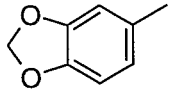
Examples 332-362



Example	R	Measured Mass (M+H)
332		494.2178
333		500.1795
334		500.1746

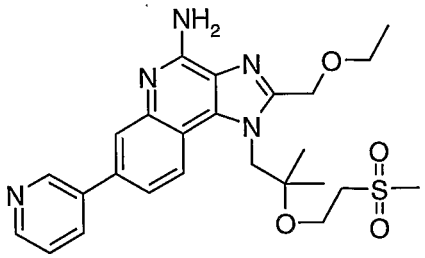
335		524.2994
336		508.2383
337		508.2341
338		510.2195
339		510.2144
340		519.2164
341		524.2298
342		528.1834
343		530.1990
344		536.2293
345		536.2316
346		536.2313

347		538.2466
348		538.2468
349		593.2872
350		554.2466
351		566.2402
352		572.1982
353		584.2515
354		586.2136
355		587.2072
356		587.2101

357		591.2743
358		593.2916
359		618.2496
360		523.2438
361		591.2751
362		538.2087

Example 363

2-Ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of methyl vinyl sulfone (3.0 g, 29 mmol) and 1-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (5.4 g, 14 mmol) in anhydrous THF (57 mL) was purged with nitrogen; solid sodium hydride (available as a 60% dispersion in mineral oil, 57 mg, 1.4 mmol) was

added. The reaction was stirred for 70 minutes at ambient temperature, at which time an analysis by HPLC indicated a ratio of product to starting material of 3:1. The reaction mixture was combined with material from another run, and water (100 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (100 mL, 50 mL). The combined organic fractions were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) to provide 7-bromo-2-ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-1*H*-imidazo[4,5-*c*]quinoline.

Part B

A modification of the method described in Example 1 Part H was used to oxidize 7-bromo-2-ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-1*H*-imidazo[4,5-*c*]quinoline (3.65 g, 7.53 mmol) with 3-chloroperoxybenzoic acid (2.2 g of 60% pure material, 7.53 mmol). The reaction was carried out in chloroform (38 mL) and allowed to proceed for one hour. The crude product was used without purification.

Part C

The material from Part B was aminated according to the method described in Part I of Example 1. The crude product was recrystallized from acetonitrile (35 mL), and the crystals were isolated by filtration, washed with acetonitrile, and dried for four hours under vacuum at 65 °C to provide 7-bromo-2-ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as gold, crystalline plates, mp 198-201 °C. Anal. Calcd for $C_{20}H_{27}BrN_4O_4S$: C, 48.10; H, 5.45; N, 11.22. Found: C, 47.96; H, 5.34; N, 11.20.

Part D

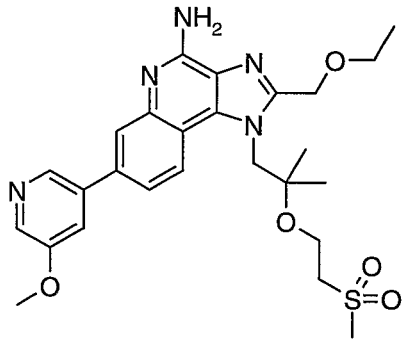
7-Bromo-2-ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.2 g, 2.4 mmol) and pyridine-3-boronic acid 1,3-propanediol cyclic ester (0.47 g, 2.9 mmol) were coupled according to the method described in Part J of Example 1. The work-up procedure used in Part F of Examples 125-135 was followed. The crude product

was purified by column chromatography on silica gel (eluting sequentially with 95:5 and 90:10 dichloromethane:methanol) followed by recrystallization from acetonitrile (52 mL/g). The crystals were isolated by filtration, washed with acetonitrile, and dried for four hours under vacuum at 65 °C to provide 0.70 g of 2-ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as white, crystalline plates, mp 202-204 °C.

Anal. Calcd for $C_{25}H_{31}N_5O_4S$: C, 60.34; H, 6.28; N, 14.07. Found: C, 60.19; H, 6.45; N, 14.02.

Example 364

2-Ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-7-(5-methoxypyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

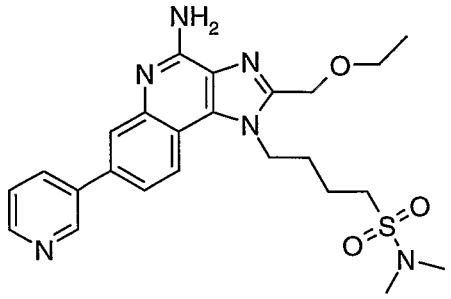


7-Bromo-2-ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.1 g, 2.2 mmol) and pyridine-5-methoxy-3-boronic acid pinacol ester (0.63 g, 2.7 mmol) were coupled according to the method described in Part J of Example 1. The work-up procedure used in Part F of Examples 125-135 was followed. The crude product was purified by HPFC (eluting with dichloromethane:methanol in a gradient from 99:1 to 85:15) followed by trituration with ethyl acetate. The crystals were isolated by filtration and dried for four hours under vacuum at 65 °C to provide 0.1 g of 2-ethoxymethyl-1-{2-[2-(methanesulfonyl)ethoxy]-2-methylpropyl}-7-(5-methoxypyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, mp 186-188 °C.

Anal. Calcd for $C_{26}H_{33}N_5O_5S$: C, 59.18; H, 6.30; N, 13.27. Found: C, 58.96; H, 6.64; N, 13.09.

Example 365

Dimethyl 4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide



Part A

A modification of the method described in Part E of Example 1 was used to treat 7-bromo-4-chloro-3-nitroquinoline (20.0 g, 69.6 mmol) with 4-amino-1-butanol (6.9 mL, 76.5 mmol). The addition of 4-amino-1-butanol was carried out at ambient temperature. The product, 4-(7-bromo-3-nitroquinolin-4-ylamino)butan-1-ol (21.1 g) was isolated as a yellow solid and used without purification.

Part B

A suspension of 4-(7-bromo-3-nitroquinolin-4-ylamino)butan-1-ol (20.75 g, 61.0 mmol) in dichloromethane (220 mL) was cooled to 0 °C; thionyl chloride (4.90 mL, 67.1 mmol) was added dropwise over a period of ten minutes. The reaction was stirred at 0 °C for five minutes, allowed to warm to ambient temperature, and stirred overnight. Aqueous sodium bicarbonate (500 mL of 50%) was slowly added. The aqueous layer was separated and extracted with dichloromethane (3 x 100 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield an orange semi-solid. An analysis by LCMS indicated the presence of starting material, and the semi-solid was dissolved in dichloromethane (150 mL) and treated with thionyl chloride (3.0 mL) as described above. Following the work-up procedure, the crude product was purified by column chromatography on

silica gel (eluting with dichloromethane:methanol in a gradient from 100:0 to 95:5) to provide 8.3 g of (7-bromo-3-nitroquinolin-4-yl)-(4-chlorobutyl)amine as a yellow solid.

Part C

A suspension of (7-bromo-3-nitroquinolin-4-yl)-(4-chlorobutyl)amine (8.05 g, 22.5 mmol) in methanol (250 mL) was cooled to 0 °C; a solution of sodium hydrosulfite (19.5 g, 112 mmol) in water (80 mL) was added dropwise over a period of 30 minutes. The reaction was stirred at ambient temperature for two hours and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (300 mL) and aqueous sodium bicarbonate (150 mL of 50%). The aqueous layer was separated and extracted with dichloromethane (2 x 50 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 7.25 g of crude 7-bromo-N^4-(4-chlorobutyl)quinoline-3,4-diamine as a light brown semi-solid.

Part D

A modification of the method described in Part C of Examples 125-135 was used to treat 7-bromo-N^4-(4-chlorobutyl)quinoline-3,4-diamine (7.25 g, 22.1 mmol) with ethoxyacetyl chloride (2.76 mL, 24.3 mmol). After the reaction was stirred for one hour, it was concentrated under reduced pressure to provide *N*-[7-bromo-4-(4-chlorobutylamino)quinolin-3-yl]-2-ethoxyacetamide hydrochloride as a yellow solid.

Part E

Aqueous sodium hydroxide (16.6 mL of 2 M, 33.2 mmol) was added to a suspension of the material from Part D in ethanol (100 mL), and the reaction was heated to 60 °C over a period of 30 minutes and stirred at 60 °C for one hour. The reaction was allowed to cool to ambient temperature and then concentrated under reduced pressure. The residue was partitioned between water (150 mL) and dichloromethane (300 mL). The aqueous layer was separated and extracted with dichloromethane (2 x 75 mL). The combined organic fractions were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column

chromatography on silica gel (eluting with ethyl acetate:chloroform in a gradient from 20:80 to 100:0) to provide 4.46 g of 7-bromo-1-(4-chlorobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline as a tan solid.

Part F

Potassium thioacetate (1.70 g, 14.9 mmol) was added in one portion to a stirred solution of 7-bromo-1-(4-chlorobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline (5.37 g, 13.5 mmol) in DMF (65 mL), and the reaction was stirred at ambient temperature for 21 hours. The DMF was removed under reduced pressure, and the residue was partitioned between dichloromethane (300 mL) and water (150 mL). The organic layer was separated, washed with brine (120 mL), dried over magnesium sulfate, filtered, and concentrated to provide 6.09 g of thioacetic acid *S*-[4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]ester as a brown solid.

Part G

Nitrogen was bubbled through a solution of thioacetic acid *S*-[4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]ester (1.93 g, 4.42 mmol) in methanol (45 mL), and then sodium methoxide (2.5 mL of 25% by weight in methanol, 11.1 mmol) was added dropwise over a period of three minutes. The yellow solution was stirred at ambient temperature for one hour and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (250 mL) and water (125 mL), and hydrochloric acid (~3 mL of 2 M) was added to adjust the mixture to pH 7. The aqueous layer was separated and extracted with dichloromethane (50 mL); the combined organic fractions were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 1.73 g of 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-thiol as a tan solid.

Part H

A solution of 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-thiol (1.73 g, 4.39 mmol) in concentrated hydrochloric acid (7.5 mL) and water (5 mL) was cooled to 0 °C. A solution of sodium chlorate (0.61 g, 5.7 mmol) in water (2.5 mL) was added dropwise with vigourous stirring over a

period of three minutes. The reaction was stirred at 0 °C for 90 minutes then diluted with dichloromethane (50 mL). Aqueous potassium carbonate (8 mL of 6M) was slowly added to adjust the mixture to pH 5. Dichloromethane (100 mL) and water (75 mL) were added, and the reaction was allowed to warm to ambient temperature with stirring. The aqueous layer was separated and extracted with dichloromethane (3 x 40 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 1.61 g of 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride as a tan solid.

Part I

Dimethylamine hydrochloride (0.60 g, 7.3 mmol) and aqueous potassium carbonate (1.46 mL of 6 M, 8.7 mmol) were sequentially added to a stirred solution of 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (1.61 g, 3.49 mmol) in dichloromethane (35 mL), and the reaction was stirred at ambient temperature for 80 minutes. Dichloromethane (180 mL) and aqueous sodium bicarbonate (60 mL) were added. The aqueous layer was separated and extracted with dichloromethane (2 x 40 mL); the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 1.49 g of dimethyl 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a tan solid.

Part J

3-Chloroperoxybenzoic acid (0.126 g of 70% pure material, 0.73 mmol) was added in one portion to a stirred solution of dimethyl 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (0.30 g, 0.63 mmol) in chloroform (7 mL), and the solution was stirred for two hours at ambient temperature. Ammonium hydroxide (2 mL) and *p*-toluenesulfonyl chloride (0.15 g, 0.76 mmol) were sequentially added, and the mixture was stirred at ambient temperature for one hour. Dichloromethane (100 mL) was added, and the mixture was washed sequentially with 2 M aqueous sodium hydroxide (2 x 30 mL), saturated aqueous sodium bicarbonate (2 x 30 mL), and brine (30 mL); dried over magnesium sulfate; filtered; and concentrated under

reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with ethyl acetate:ethanol in a gradient from 100:0 to 80:20) followed by recrystallization from dichloromethane:heptane. The crystals were dried for two hours under vacuum at 40 °C to provide 0.185 g of dimethyl 4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white solid, mp 193 °C.

Anal. Calcd for $C_{19}H_{26}BrN_5O_3S$: C, 47.11; H, 5.41; N, 14.46. Found: C, 46.85; H, 5.48; N, 14.14.

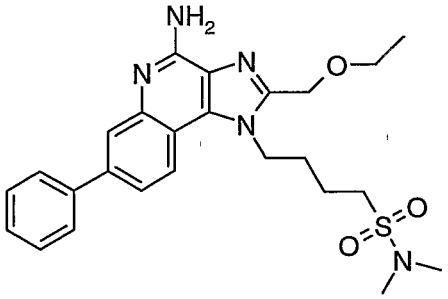
Part K

Dimethyl 4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (1.00 g, 2.06 mmol), which was prepared in a separate run, and pyridine-3-boronic acid 1,3-propanediol ester (0.40 g, 2.5 mmol) were coupled according to the method described in Part J of Example 1. The reaction was heated at reflux for 14 hours, and the work-up procedure used in Part F of Examples 125-135 was followed. The crude product was purified by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 80:20) and then triturated sequentially with dichloromethane and methanol, isolated by filtration, and dried for two days under high vacuum at 140 °C to provide 0.695 g of dimethyl 4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide as yellow needles, mp 205-206 °C.

Anal. Calcd for $C_{24}H_{30}N_6O_3S$: C, 59.73; H, 6.27; N, 17.41. Found: C, 59.49; H, 6.24; N, 17.36.

Example 366

Dimethyl 4-[4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide

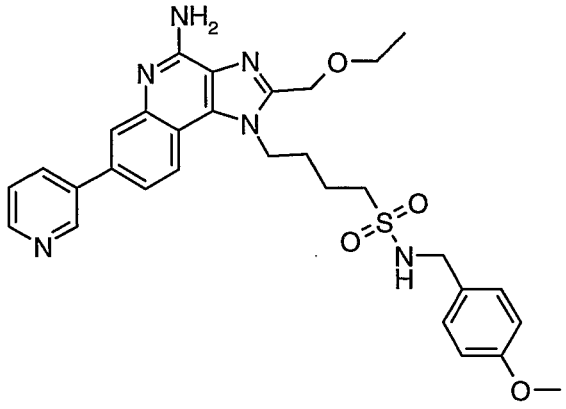


Dimethyl 4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (0.66 g, 1.4 mmol) and phenyl boronic acid (0.20 g, 1.6 mmol) were coupled according to the method described in Part J of Example 1. The reaction was heated at reflux for 14 hours, and the work-up procedure used in Part F of Examples 125-135 was followed. The crude product was recrystallized from methanol and then purified by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 100:0 to 90:10). The solid was then purified by HPFC to provide 0.14 g of dimethyl 4-[4-amino-2-ethoxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide as Off-white needles, mp 207-208 °C.

Anal. Calcd for $C_{25}H_{31}N_5O_3S$: C, 61.56; H, 6.55; N, 14.36. Found: C, 61.65; H, 6.67; N, 14.30.

Example 367

4-Methoxybenzyl 4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide



Part A

Over a period of three minutes, *p*-methoxybenzylamine (1.9 mL, 15 mmol) was added dropwise to a stirred solution of 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (2.9 g, 6.1 mmol), prepared according to the methods described in Parts A-H of Example 365, in dichloromethane (60 mL). The reaction was stirred at ambient temperature for 90 minutes then diluted with dichloromethane (150 mL) and brine (100 mL). The aqueous layer was separated and extracted with dichloromethane (2 x 30 mL); the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with dichloromethane (30 mL) to provide a white solid, which was isolated by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 90:10 to 20:80) to provide a white solid, which was triturated with dichloromethane and isolated by filtration. The solids were combined to yield 1.92 g of 4-methoxybenzyl 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white solid.

Part B

4-Methoxybenzyl 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide was oxidized and then aminated according to the general method described in Part J of Example 365. The oxidation

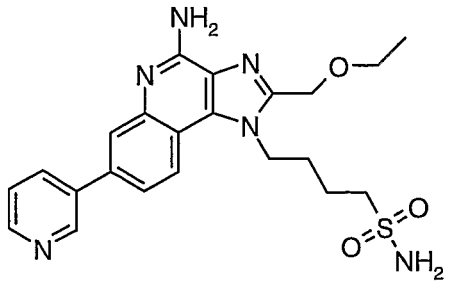
reaction was stirred for five hours, and the amination reaction was stirred overnight. The crude product was purified twice by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 80:20) to provide 0.80 g of 4-methoxybenzyl 4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide. This material was mixed with material from another run.

Part C

4-Methoxybenzyl 4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (1.16 g, 2.0 mmol) and pyridine-3-boronic acid (0.30 g, 2.4 mmol) were coupled according to the method described in Part J of Example 1. The reaction was heated at reflux for 14 hours, at which time additional pyridine-3-boronic acid (0.3 equivalent) was added and the reaction was heated for an additional five hours. The work-up procedure used in Part F of Examples 125-135 was followed. The crude product was purified by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) and then triturated with methanol, isolated by filtration, and dried for 20 hours under high vacuum at 140 °C to provide 0.62 g of 4-methoxybenzyl 4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide as a beige powder, mp 230-231.5 °C. Anal. Calcd for $C_{30}H_{34}N_6O_4S$: C, 62.70; H, 5.96; N, 14.62. Found: C, 62.39; H, 6.06; N, 14.56.

Example 368

4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide



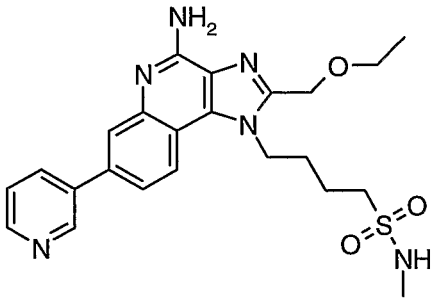
A solution of 4-methoxybenzyl 4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide (0.50 g, 0.88 mmol)

in trifluoroacetic acid (5 mL) was stirred at ambient temperature for four hours and then concentrated under reduced pressure. The residue was dissolved in methanol and concentrated under reduced pressure; this process was repeated three times. The residue was then suspended in water, and 2 M aqueous sodium hydroxide was added to adjust to pH 7. The mixture was stirred for 30 minutes, and the resulting solid was isolated by filtration, washed with water, and purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 30:70). The purified product was dried overnight under high vacuum at 80 °C to provide 0.31 g of 4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide as tan needles, mp 250-251.5 °C.

Anal. Calcd for $C_{22}H_{26}N_6O_3S$: C, 58.13; H, 5.77; N, 18.49. Found: C, 57.89; H, 5.44; N, 18.16.

Example 369

Methyl 4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide



Part A

The method described in Part I of Example 365 was used to treat 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonyl chloride (1.61 g, 3.49 mmol), prepared according to the methods described in Parts A-H of Example 365, with methylamine hydrochloride (0.50 g, 7.3 mmol) and aqueous potassium carbonate (1.3 mL of 6 M, 7.7 mmol) to provide 1.4 g of methyl 4-[7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide as a tan solid.

Part B

Methyl 4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide was oxidized and then aminated according to the general method described in Part J of Example 365. The oxidation reaction was stirred for three hours, and the amination reaction was stirred for 90 minutes. The crude product was recrystallized from a mixture of dichloromethane, heptane, and a trace of methanol and isolated by filtration. The mother liquor was concentrated and purified by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 80:20) and then triturated with dichloromethane and isolated by filtration. The products were dried overnight under high vacuum at 140 °C to provide a total of 0.86 g of methyl 4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide as a white solid, mp 199-200 °C.

Anal. Calcd for $C_{18}H_{24}BrN_5O_3S$: C, 45.96; H, 5.14; N, 14.89. Found: C, 46.02; H, 4.85; N, 14.65.

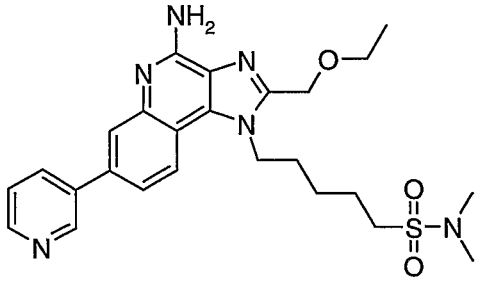
Part C

Methyl 4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butane-1-sulfonamide (0.78 g, 1.7 mmol) and pyridine-3-boronic acid 1,3-propanediol cyclic ester (0.33 g, 2.0 mmol) were coupled according to the method described in Part J of Example 1. The reaction was heated at reflux for 15 hours, at which time additional pyridine-3-boronic acid 1,3-propanediol cyclic ester, palladium acetate, and triphenylphosphine were added, and the reaction was heated for an additional three hours. The work-up procedure used in Part F of Examples 125-135 was followed. The crude product was purified twice by column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 70:30) and then triturated with methanol, isolated by filtration, and dried for eight hours under high vacuum at 100 °C to provide 0.78 g of methyl 4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butane-1-sulfonamide as off-white needles, mp 216-218 °C..

Anal. Calcd for $C_{23}H_{28}N_6O_3S \bullet 0.23\ H_2O$: C, 58.44; H, 6.07; N, 17.78. Found: C, 58.08; H, 5.97; N, 17.71.

Example 370

Dimethyl 5-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentane-1-sulfonamide



Part A

The method described in Part A of Example 365 was used to treat 7-bromo-4-chloro-3-nitroquinoline (20.0 g, 69.5 mmol) with 4-amino-1-pentanol (7.9 g, 76 mmol) to provide 24.0 g of 5-(7-bromo-3-nitroquinolin-4-ylamino)pentan-1-ol as a yellow solid.

Part B

A suspension of 5-(7-bromo-3-nitroquinolin-4-ylamino)pentan-1-ol (0.92 g, 2.6 mmol) in dichloromethane (13 mL) was cooled to 0 °C; thionyl chloride was added dropwise. The reaction was stirred for five minutes at 0 °C then allowed to warm to ambient temperature and stirred overnight. Saturated aqueous sodium bicarbonate (25 mL) was slowly added followed by water (25 mL). The aqueous layer was separated and extracted with dichloromethane (3 x 50 mL), and the combined organic fractions were dried over magnesium sulfate and concentrated under reduced pressure to provide 0.91 g of (7-bromo-3-nitroquinolin-4-yl)-(5-chloropentyl)amine as a yellow semisolid.

Part C

The methods described in Parts C-E of Example 365 were used to convert (7-bromo-3-nitroquinolin-4-yl)-(5-chloropentyl)amine to 7-bromo-1-(5-chloropentyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline. The crude product was purified twice by column chromatography on silica gel (eluting with chloroform:methanol in a gradient from 100:0 to 90:10).

Part D

Thiourea (0.29 g, 3.8 mmol) and potassium iodide (0.052 g, 3.1 mmol) were sequentially added to a suspension of 7-bromo-1-(5-chloropentyl)-2-

ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline (1.3 g, 3.2 mmol) in DMF (15 mL), and the reaction was heated at 110 °C for 24 hours. The DMF was removed under reduced pressure, and the residue was partitioned between saturated aqueous sodium bicarbonate (40 mL) and dichloromethane (50 mL). The mixture was adjusted to pH 7 with the addition of 10% hydrochloric acid. Product remained on the walls of the reaction flask and was dissolved with methanol. The resulting solution was concentrated under reduced pressure to provide a solid. The aqueous layer was concentrated under reduced pressure, and the resulting solid was triturated with methanol and isolated by filtration. The filtrate was concentrated under reduced pressure, and the residue was triturated and isolated as described above. The isolated solids were combined and dried under high vacuum to provide 1.49 g of 2-[5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentyl]isothiourea hydrochloride as a yellow solid.

Part E

A solution of 2-[5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentyl]isothiourea hydrochloride (1.49 g, 3.16 mmol) in 7 M hydrochloric acid (8 mL) was cooled to 0 °C. A solution of sodium chlorate (0.44 g, 4.1 mmol) in water (1.0 mL) was added dropwise with stirring, and the reaction was stirred at 0 °C for one hour. A precipitate formed and was isolated by filtration, washed with ice-cold water (4 x 4 mL), and dried under high vacuum to provide 0.92 g of 5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonyl chloride as a yellow solid.

Part F

The method described in Part I of Example 365 was used to treat 5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonyl chloride (0.91 g, 1.9 mmol) with dimethylamine hydrochloride (0.33 g, 4.0 mmol). The crude product was purified by HPFC (eluting with ethyl acetate:methanol in a gradient from 100:0 to 90:10) to provide 0.57 g of dimethyl 5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide as a yellow solid.

Part G

Dimethyl 5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide was oxidized and aminated according to the methods described in Part J of Example 365. The crude product was purified twice by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 90:10) and then triturated with ethyl acetate, isolated by filtration, washed with ethyl acetate (2 x 1 mL), and dried for several hours under high vacuum at 150 °C to provide dimethyl 5-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide as a yellow solid.

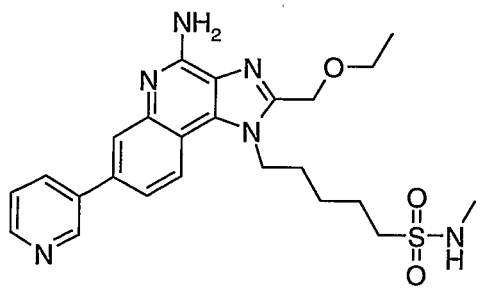
Part H

Dimethyl 5-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide (0.26 g, 0.53 mmol) and pyridine-3-boronic acid (0.78 g, 0.63 mmol) were coupled according to the method described in Part J of Example 1. The reaction was heated at 100 °C for 31 hours, at which time additional palladium acetate (0.002 equivalent) was added. Heating was resumed for 14 hours, and then additional pyridine-3-boronic acid (0.3 equivalent) was added. The reaction was heated for another 22 hours. The work-up procedure used in Part F of Examples 125-135 was followed. The crude product was purified twice by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) and then triturated with ethyl acetate and isolated by filtration. The product was finally recrystallized from isopropanol, isolated by filtration, and dried for eight hours under high vacuum at 100 °C to provide 0.090 g of dimethyl 5-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentane-1-sulfonamide as a white powder, mp 159-160°C.

Anal. Calcd for $C_{25}H_{32}N_6O_3S$: C, 60.46; H, 6.49; N, 16.92. Found: C, 60.33; H, 6.56; N, 16.81.

Example 371

Methyl 5-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentane-1-sulfonamide



Part A

The method described in Part I of Example 365 was used to treat 5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonyl chloride (1.11 g, 2.33 mmol) with methylamine hydrochloride (0.33 g, 4.9 mmol). The reaction was stirred overnight, and additional methylamine hydrochloride (0.3 equivalent) and 6 M potassium carbonate (0.4 equivalent) were added. The reaction was stirred for an additional four hours. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) to provide 0.80 g of methyl 5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide as a white solid.

Part B

Methyl 5-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide was oxidized and aminated according to the methods described in Part J of Example 365. The oxidation reaction was stirred for three hours, and the amination reaction was stirred for 90 minutes. The product precipitated from the reaction mixture and was isolated by filtration. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) to provide methyl 5-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide as a white solid.

Part C

Methyl 5-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentane-1-sulfonamide (0.47 g, 0.97 mmol) was coupled with pyridine-3-boronic acid (0.14 g, 1.2 mmol) according to the methods described in Part J of Example 1 and Part H of Example 370. The crude product was purified twice by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) and then recrystallized from methanol, isolated by filtration, and dried for 5 days under high vacuum at 100-140 °C to provide 0.13 g of methyl 5-[4-

amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentane-1-sulfonamide as a white powder, mp 191-192°C.

Anal. Calcd for $C_{24}H_{30}N_6O_3S$: C, 59.73; H, 6.27; N, 17.41. Found: C, 59.48; H, 6.58; N, 17.56.

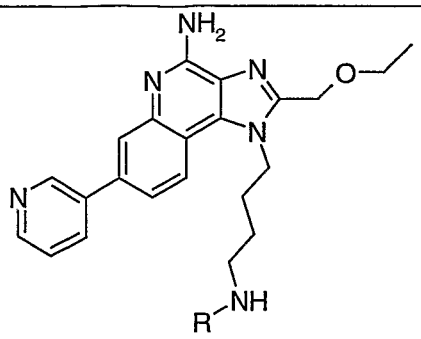
Examples 372-376

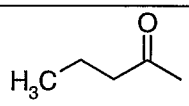
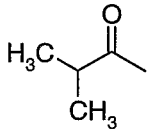
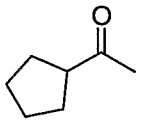
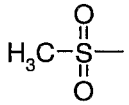
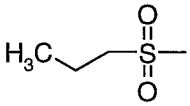
Part A

A solution of *tert*-butyl {4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate (40.35 g, 82.24 mmol) in concentrated hydrochloric acid (400 mL) was stirred for one hour, filtered, and concentrated under reduced pressure. The residue was dissolved in a minimal amount of water, and 50% aqueous sodium hydroxide was added to adjust the solution to pH 14. Chloroform (1.2 L) and a mixture of saturated aqueous sodium bicarbonate and 1% aqueous sodium carbonate (600 mL) were added; the mixture was stirred for 30 minutes. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to provide 36.48 g of 1-(4-aminobutyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a light yellow solid.

Part B

Triethylamine (1.39 mL, 10.0 mmol) was added to a solution of 1-(4-aminobutyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3.00 g, 7.70 mmol) in chloroform (150 mL); the reagent (1.1 equivalents) listed in the table below was then added. The reaction was stirred for one hour or until completion; additional triethylamine and the indicated reagent were added as need until the reaction was complete. Deionized water (15-20 mL) was added, and the mixture was stirred for five minutes. The organic layer was separated, washed with 1% aqueous sodium carbonate, optionally dried with sodium sulfate and filtered, and concentrated under reduced pressure. The crude product was recrystallized from the solvent listed in the table below and dried overnight in a drying oven to provide the compound with the structure shown below.



Example	Reagent	Recrystallization solvent	R
372	Butyryl chloride	Acetonitrile:water 83:17	
373	Isobutyryl chloride	Isopropanol then acetonitrile:water	
374	Cyclopentanecarbonyl chloride	Acetonitrile:water, isopropanol, methyl acetate, then isopropanol	
375	Methanesulfonic anhydride	Precipitated during work-up, no recrystallization done	
376	1-Propanesulfonyl chloride	Isopropanol then acetonitrile:water 75:25	

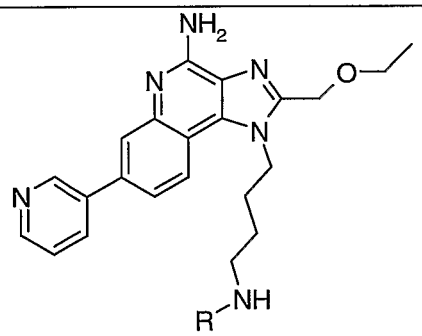
Example	Name	Form	mp (°C)	Anal.
372	*N*-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}butyramide	White solid	150-152	Calcd for $C_{26}H_{32}N_6O_2$: C, 67.80; H, 7.00; N, 18.25. Found: C, 67.51; H, 7.29; N, 18.18.
373	*N*-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-2-methylpropanamide	White solid	200-202	Calcd for $C_{26}H_{32}N_6O_2$: C, 67.80; H, 7.00; N, 18.25. Found: C, 67.47; H, 7.09; N, 18.16.
374	*N*-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide	White solid	196-198	Calcd for $C_{28}H_{34}N_6O_2 \bullet 0.25 H_2O$: C, 68.48; H, 7.08; N, 17.11. Found: C, 68.28; H, 7.36; N, 17.00.
375	*N*-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide	White solid	186-188	Calcd for $C_{23}H_{28}N_6O_3S \bullet 0.25 H_2O$: C, 58.39; H, 6.07; N, 17.76. Found: C, 58.31; H, 5.75; N, 17.72.

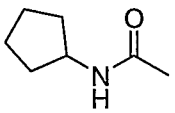
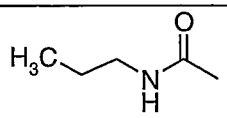
376	*N*-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}propane-1-sulfonamide	Off-white solid	178-180	Calcd for $C_{25}H_{32}N_6O_3S$: C, 60.46; H, 6.49; N, 16.92. Found: C, 60.22; H, 6.42; N, 16.77.

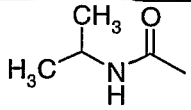
Examples 377-379

The isocyanate indicated in the table below was added slowly to a solution of 1-(4-aminobutyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1 equivalent) in chloroform (20-50 mL/g). A precipitate formed within five minutes or formed upon cooling the reaction mixture to ~0 °C after 15 minutes. The precipitate was isolated by filtration and dried overnight in an oven. The solid was slurried with the solvent(s) listed in the table below, isolated by filtration, and dried overnight in an oven to provide the product with the structure shown in the table below.

Examples 377-379



Example	Isocyanate	Purification solvent	R
377	Cyclopentyl isocyanate	Acetonitrile:water 75:25	
378	Propyl isocyanate	Not used	

379	Isopropyl isocyanate	Hot isopropanol	

Example	Name	Form	mp (°C)	Anal.
377	*N*-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-cyclopentylurea	White solid	190-192	Calcd for $C_{28}H_{35}N_7O_2$: C, 67.04; H, 7.03; N, 19.55. Found: C, 66.76; H, 7.01; N, 19.46.
378	*N*-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-propylurea	White solid	191-193	Calcd for $C_{26}H_{33}N_7O_2$: C, 65.66; H, 6.99; N, 20.62. Found: C, 65.84; H, 7.43; N, 20.66.
379	*N*-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-(1-methylethyl)urea	White solid	192-194	Calcd for $C_{26}H_{33}N_7O_2$: C, 65.66; H, 6.99; N, 20.62. Found: C, 65.83; H, 7.39; N, 20.52.

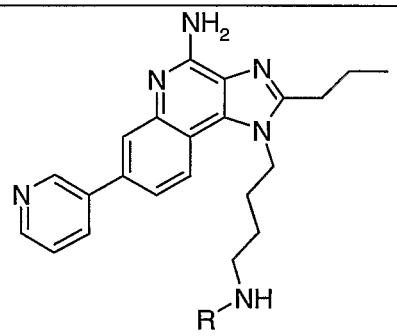
Examples 380-382

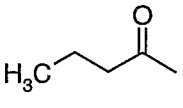
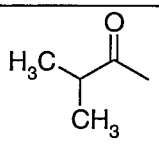
A solution of *tert*-butyl {4-[4-amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate (41.92 g, 88.32 mmol) in concentrated hydrochloric acid (210 mL) was stirred for ten minutes, and 50% aqueous sodium hydroxide was added to adjust the solution to pH 14. Chloroform (2.0 L) and a mixture of saturated aqueous sodium bicarbonate and 1% aqueous sodium carbonate (300 mL) were added. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to provide a yellow solid. The aqueous phase was treated with sodium chloride and chloroform (400 mL), and the mixture was stirred overnight. The organic layer

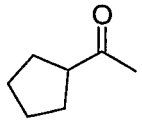
was separated, dried over sodium sulfate, and concentrated under reduced pressure to provide a yellow solid. The two solids were combined to yield 28.77 g of 1-(4-aminobutyl)-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a light yellow solid.

Triethylamine (1.34 mL, 9.61 mmol) was added to a solution of 1-(4-aminobutyl)-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3.00 g, 8.01 mmol) in chloroform (141 mL); the solution was then cooled to 0 °C. A cold solution of the reagent (1.0 equivalent) listed in the table below in chloroform (9 mL) was then added. The reaction was stirred for 15 or 90 minutes, and deionized water (25 mL) was added. A precipitate formed and was isolated by filtration and dried overnight in a drying oven. The crude product was triturated with the solvent(s) listed in the table below, isolated by filtration, and dried overnight in a drying oven to provide the compound with the structure shown below.

Examples 380-382



Example	Reagent	Purification solvent	R
380	Butyryl chloride	Chloroform (10 mL/g) and 1% aqueous sodium carbonate (3 mL/g)	
381	Isobutyryl chloride	Not used	

382	Cyclopentanecarbonyl chloride	Chloroform (10 mL/g) then recrystallized from isopropanol (6 mL/g)	

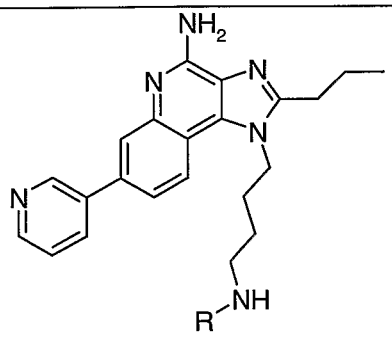
Example	Name	Form	mp (°C)	Anal.
380	*N*-{4-[4-Amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}butyramide	White solid	144-146	Calcd for $C_{26}H_{32}N_6O•2H_2O$: C, 64.98; H, 7.55; N, 17.49. Found: C, 64.53; H, 7.08; N, 17.44.
381	*N*-{4-[4-Amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-2-methylpropanamide	White solid	168-170	Calcd for $C_{26}H_{32}N_6O•0.25H_2O$: C, 69.54; H, 7.29; N, 18.71. Found: C, 69.45; H, 7.67; N, 18.65.
382	*N*-{4-[4-Amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide	White solid	180-182	Calcd for $C_{28}H_{34}N_6O•1.5H_2O$: C, 67.58; H, 7.49; N, 16.89. Found: C, 67.51; H, 7.72; N, 17.09.

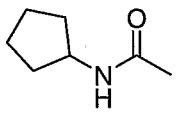
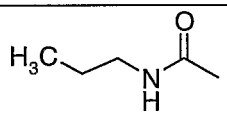
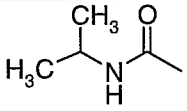
Examples 383-385

A solution of 1-(4-aminobutyl)-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1 equivalent) in chloroform (18 mL/g) was

cooled to 0 °C; a cold solution of the isocyanate indicated in the table below (1.05 equivalents) in chloroform (2 mL/g) was added. A precipitate formed within ten minutes or formed upon cooling the reaction mixture to ~0 °C for 30 minutes. The precipitate was isolated by filtration and dried overnight in an oven. The solid was from 1:1 acetonitrile:water, isolated by filtration, and dried for five days in an oven at 63 °C to provide the product with the structure shown in the table below.

Examples 383-385

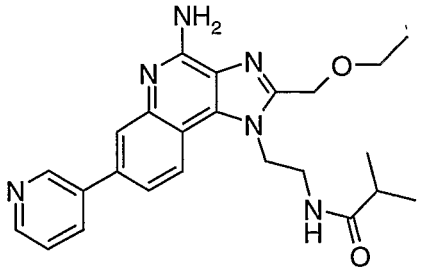


Example	Isocyanate	R
383	Cyclopentyl isocyanate	
384	Propyl isocyanate	
385	Isopropyl isocyanate	

Example	Name	Form	mp (°C)	Anal.
383	*N*-{4-[4-Amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-cyclopentylurea	White solid	181-183	Calcd for $C_{28}H_{35}N_7O$•1.5 H_2O: C, 65.60; H, 7.47; N, 19.13. Found: C, 65.44; H, 7.61; N, 19.09.
384	*N*-{4-[4-Amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-propylurea	White solid	184-185	Calcd for $C_{26}H_{33}N_7O$•0.25 H_2O: C, 67.29; H, 7.28; N, 21.13. Found: C, 67.15; H, 7.56; N, 21.41.
385	*N*-{4-[4-Amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-(1-methylethyl)urea	White solid	173-175	Calcd for $C_{26}H_{33}N_7O$•1.25 H_2O: C, 64.77; H, 7.42; N, 20.34. Found: C, 64.36; H, 7.78; N, 20.21.

Example 386

N-{2-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-2-methylpropanamide



Part A

A solution of 7-bromo-4-chloro-3-nitroquinoline (140.00 g, 486.96 mmol) in chloroform (2.8 L) was cooled to 0 °C. Triethylamine (82.0 mL, 588 mol) and ethylenediamine (35.75 mL, 535.6 mmol) were sequentially added; the resulting mixture was stirred for one hour at 0 °C then allowed to warm to ambient temperature and stirred for two hours. Additional ethylenediamine (0.1 equivalent) was added, and the reaction was stirred for an additional 1.75 hours. Additional triethylamine (88.0 mL, 631 mmol) followed by a solution of di-*tert*-butyl dicarbonate (180.0 mL, 779.1 mmol) in chloroform (320 mL) were added, and the reaction was stirred overnight at ambient temperature. Water (750 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated and washed with 1% aqueous sodium carbonate (2 x 750 mL), dried over sodium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure. The resulting solid was triturated with hot acetonitrile (5 mL/g at 95 °C), cooled in an ice bath, and isolated by filtration to provide 165.0 g of *tert*-butyl [2-(7-bromo-3-nitroquinolin-4-ylamino)ethyl]carbamate as a light yellow solid.

Part B

A solution of *tert*-butyl [2-(7-bromo-3-nitroquinolin-4-ylamino)ethyl]carbamate (165.0 g, 401.2 mmol) in acetonitrile (3.3 L) and isopropanol (990 mL) and 5% platinum on carbon (13.2 g) were added to a Parr vessel, which was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) overnight. The mixture was filtered through a layer of CELITE filter aid, and the filtrate was concentrated under reduced pressure to provide 139.29 g of *tert*-butyl [2-(3-amino-7-bromoquinolin-4-ylamino)ethyl]carbamate as a yellow solid. The product was suspended in a mixture of dichloromethane (4 mL/g) and chloroform (8 mL/g), and the suspension was divided into two equal portions.

Part C

Ethoxyacetyl chloride (25.44 g, 182.7 mmol) in chloroform (50 mL) was added to one portion of the suspension from Part B. The resulting brown solution was stirred for 30 minutes and then concentrated under reduced pressure.

Part D

Triethylamine (101.85 mL, 730.7 mmol) was added to a suspension of the material from Part C in ethanol (1.1 L); the mixture was heated at reflux for two hours, allowed to stand over three days, and concentrated under reduced pressure. The residue was partitioned between chloroform (1.2 L) and water (400 mL). The organic layer was separated, washed with brine (2 x 400 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was triturated with acetonitrile (10 mL/g) at 95 °C, isolated by filtration, and dried for three days to provide 51.48 g of *tert*-butyl [2-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as a white solid.

Part E

A modification of the method described in Example 1 Part H was used to oxidize *tert*-butyl [2-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (36.48 g, 81.18 mmol) with 3-chloroperoxybenzoic acid (36.31 g of 77% pure material, 105.5 mmol). The reaction was carried out in chloroform (370 mL) and allowed to proceed for 30 minutes. The crude product was used without purification.

Part F

The material from Part E was aminated according to the method described in Part I of Example 1; the reaction was complete after one hour. The crude product was triturated with acetonitrile (7 mL/g) at 95 °C, and the resulting solid was isolated by filtration to provide 26.89 g of *tert*-butyl [2-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as a fluffy, white solid.

Part G

tert-Butyl [2-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (21.80 g, 46.94 mmol) and 3-pyridylboronic acid (6.64 g, 54.0 mmol) were coupled according to the method described in Part J of Example 1. Palladium (II) acetate was added as a 5 mg/mL solution in toluene. The reaction was terminated after 4.5 hours, and the work-up procedure described in Part F of Examples 125-135 was followed. The crude product was recrystallized from acetonitrile (12 mL/g) to provide 10.80 g of *tert*-butyl {2-[2-

ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}carbamate as a white solid.

Part H

The method described in Part A of Examples 372-376 was used to convert *tert*-butyl {2-[2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}carbamate (10.80 g, 23.34 mmol) to 8.38 g of 1-(2-aminoethyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid.

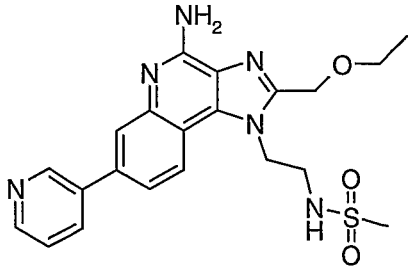
Part I

1-(2-Aminoethyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.00 g, 5.50 mmol) was treated with triethylamine (1.00 mL, 7.20 mmol) and isobutyryl chloride (0.64 mL, 6.10 mmol) according to the method described in Part B of Examples 372-376. The crude product was recrystallized from 93:7 acetonitrile:water and then from isopropanol (7.3 mL/g) and dried for two hours in a drying oven to provide 0.78 g of *N*-{2-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-2-methylpropanamide as a white solid, mp 213-215 °C.

Anal. Calcd for $C_{24}H_{28}N_6O_2 \bullet 0.75\ H_2O$: C, 64.63; H, 6.67; N, 18.84. Found: C, 64.66; H, 6.54; N, 18.71.

Example 387

N-{2-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}methanesulfonamide



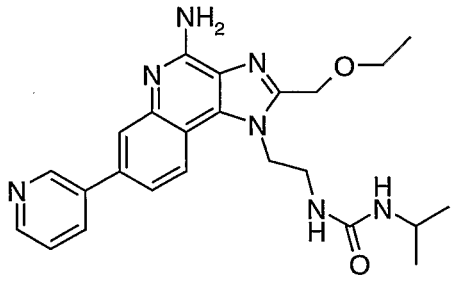
A solution of 1-(2-aminoethyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.00 g, 5.50 mmol) in chloroform (40 mL) was treated with triethylamine (1.62 mL, 11.6 mmol) and methanesulfonyl chloride (0.47 mL, 6.05 mmol). The reaction was stirred for 1.5 hours, and additional

methanesulfonyl chloride (2 equivalents) was added. The reaction was stirred for 30 minutes, and then deionized water (15 mL) was added. A precipitate formed and was isolated by filtration, triturated once with methanol and twice with chloroform and 1% aqueous sodium carbonate, isolated by filtration, and dried overnight in an oven to provide 0.65 g of *N*-{2-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}methanesulfonamide as a white solid, mp 233-235 °C.

Anal. Calcd for $C_{21}H_{24}N_6O_3S \bullet 0.5\ H_2O$: C, 56.11; H, 5.61; N, 18.69. Found: C, 56.02; H, 5.71; N, 18.64.

Example 388

N-{2-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-(1-methylethyl)urea

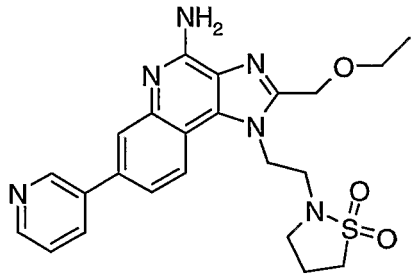


A solution of 1-(2-aminoethyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.50 g, 6.90 mmol) in chloroform (50 mL) was treated with isopropyl isocyanate (0.65 mL, 6.9 mmol) according to the method described in Examples 377-379. The crude product was purified by column chromatography on silica gel (eluting with 94:6 chloroform:methanol) followed by trituration with acetonitrile (15 mL/g) at 95 °C. The mixture was cooled in an ice bath, isolated by filtration, and dried for one hour in a vacuum oven at 100 °C to provide 0.88 g of *N*-{2-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-(1-methylethyl)urea as a white solid, mp 194-196 °C.

Anal. Calcd for $C_{24}H_{29}N_7O_2$: C, 64.41; H, 6.53; N, 21.91. Found: C, 64.34; H, 6.82; N, 22.05.

Example 389

1-[2-(1,1-Dioxo-1-isothiazolidin-2-yl)ethyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

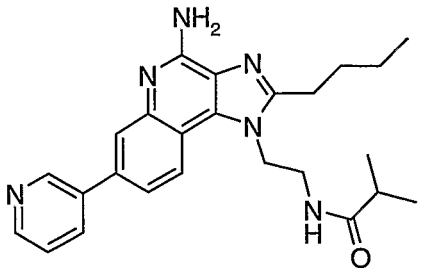


3-Chloropropanesulfonyl chloride (2.52 mL, 20.7 mmol) was added to a solution of 1-(2-aminoethyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.50 g, 6.90 mmol) in chloroform (50 mL) in two portions over a period of two hours, and the reaction was stirred overnight at ambient temperature. Additional 3-chloropropanesulfonyl chloride (1.72 mL, 14.1 mmol) was added followed by triethylamine (2.02 mL, 14.9 mmol) to drive the reaction to completion. Chloroform (50 mL) and water (30 mL) were added, and the mixture was stirred for five minutes. A precipitate formed, was isolated by filtration, and was mixed with DMF (66 mL) and DBU (2.06 mL, 13.8 mmol). The resulting solution was stirred for three days at ambient temperature and then combined with water (660 mL) and chloroform (400 mL). The organic layer was separated and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 95:5 chloroform:methanol). The resulting solid was triturated with methanol at 80 °C, cooled in an ice bath, isolated by filtration, and dried overnight in a vacuum oven to provide 0.28 g of 1-[2-(1,1-dioxo-1-isothiazolidin-2-yl)ethyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 244-246 °C.

Anal. Calcd for $C_{23}H_{26}N_6O_3S \bullet 0.11\ H_2O$: C, 58.96; H, 5.64; N, 17.94. Found: C, 58.86; H, 5.69; N, 17.90.

Example 390

N-{2-[4-Amino-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-2-methylpropanamide



Part A

Valeryl chloride (21.68 mL, 182.6 mmol) in chloroform (50 mL) was added to one portion of the suspension from Part B of Example 386. The resulting brown solution was stirred for 30 minutes and then concentrated under reduced pressure.

Part B

A solution of sodium hydroxide (21.92 g, 274.0 mmol) in water (110 mL) was added to a suspension of the material from Part A in ethanol (640 mL); the mixture was heated at reflux for four hours and then concentrated under reduced pressure. The residue was partitioned between chloroform (1.2 L) and deionized water (400 mL). The mixture was stirred for 30 minutes. The organic fraction was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was triturated with isopropanol at 95 °C, isolated by filtration, and dried on the filter funnel to provide 39.78 g of *tert*-butyl [2-(7-bromo-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as a pinkish-gray solid.

Part C

tert-Butyl [2-(7-bromo-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (24.78 g, 55.4 mmol) was oxidized and then aminated according to the methods described in Parts E and F of Example 386. After purification 19.13 g of *tert*-butyl [2-(4-amino-7-bromo-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate was obtained as a gray solid.

Part D

tert-Butyl [2-(4-amino-7-bromo-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (14.09 g, 30.5 mmol) and 3-pyridylboronic acid (4.31 g, 35.0 mmol) were coupled according to the method described in Part G of Example 386. The reaction was heated for 2.5 hours. The crude product was triturated with toluene (15 mL/g) at 123 °C and isolated by filtration to provide 11.31 g of *tert*-butyl {2-[2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}carbamate as a white solid.

Part E

The method described in Part A of Examples 372-376 was used to convert *tert*-butyl {2-[2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}carbamate (11.31 g, 24.56 mmol) to 1-(2-aminoethyl)-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine.

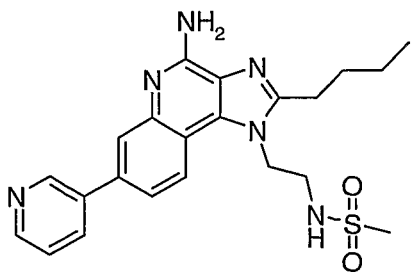
Part F

1-(2-Aminoethyl)-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.00 g, 5.50 mmol) was treated with triethylamine (1.01 mL, 7.26 mmol) and isobutyryl chloride (0.64 mL, 6.10 mmol) according to the method described in Part B of Examples 372-376. The crude product was recrystallized from isopropanol (4 mL/g) and then triturated with acetonitrile (12.5 mL/g), isolated by filtration, and dried overnight in a drying oven to provide 0.61 g of *N*-{2-[4-amino-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-2-methylpropanamide as a white solid, mp 228-230 °C.

Anal. Calcd for $C_{25}H_{30}N_6O$: C, 69.74; H, 7.02; N, 19.52. Found: C, 69.37; H, 6.97; N, 19.60.

Example 391

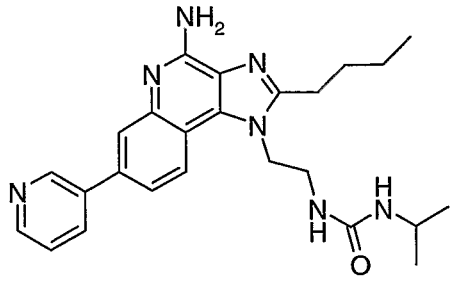
N-{2-[4-Amino-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}methanesulfonamide



The method described in Example 387 was used to convert 1-(2-aminoethyl)-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine to *N*-{2-[4-amino-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}methanesulfonamide.

Example 392

N-{2-[4-Amino-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-(1-methylethyl)urea

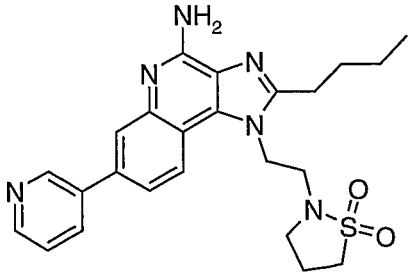


Isopropyl isocyanate (0.29 mL, 3.1 mmol) was added slowly to a suspension of 1-(2-aminoethyl)-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.13 g, 3.1 mmol) in chloroform (113 mL). A precipitate formed within 15 minutes, was isolated by filtration, and was dried overnight in an oven to provide 0.66 g of *N*-{2-[4-amino-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-(1-methylethyl)urea as a white solid, mp 240-241 °C.

Anal. Calcd for $C_{25}H_{31}N_7O$: C, 67.39; H, 7.01; N, 22.00. Found: C, 67.24; H, 7.08; N, 21.90.

Example 393

1-[2-(1,1-Dioxo-1-isothiazolidin-2-yl)ethyl]-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



The method described in Example 389 was used to convert 1-(2-aminoethyl)-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (4.00 g, 11.1 mmol) to 1.05 g of 1-[2-(1,1-dioxo-1-isothiazolidin-2-yl)ethyl]-2-butyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, which was isolated as a white solid, mp 290-292 °C.

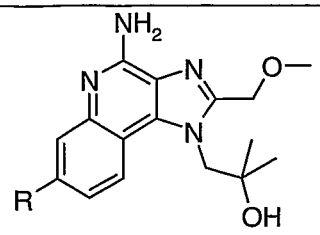
Anal. Calcd for $C_{24}H_{28}N_6O_2S \bullet 0.06\ H_2O$: C, 61.90; H, 6.09; N, 18.05. Found: C, 61.52; H, 6.03; N, 18.05.

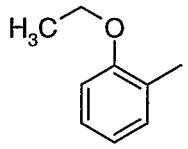
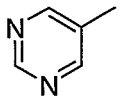
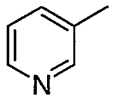
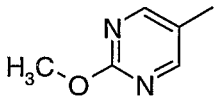
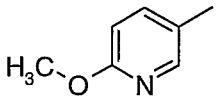
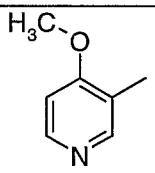
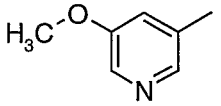
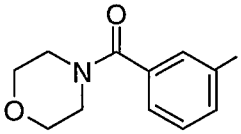
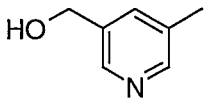
Examples 394-403

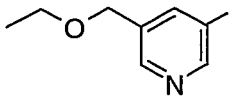
The methods described in Parts C, D, and E of Examples 125-135 were used to convert 1-(3-amino-7-bromoquinolin-4-ylamino)-2-methylpropan-2-ol to 1-(4-amino-7-bromo-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol. Methoxyacetyl chloride was used in lieu of ethoxyacetyl chloride in Part C.

1-(4-Amino-7-bromo-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol and the boronic acid or boronic acid ester from the table below were coupled according to the procedure described in Part F of Examples 125-135. After the work-up procedure, the crude product was purified by HPFC (eluting with chloroform:methanol in a gradient from 100:0 to 70:30). The resulting product was dissolved in dichloromethane and concentrated under reduced pressure until a precipitate began to form. Hexanes were added, and the resulting solid was isolated by filtration and dried overnight under vacuum at 70 °C to provide the compound shown in the table below. For Example 399, the solid isolated by filtration was triturated with hot acetonitrile, isolated by filtration, and dried under vacuum. For Example 402, the product from the coupling reaction was deprotected according to the method described in Part C of Example 150 to provide the product shown in the table below. The purification and characterization of Example 403 is given below the following tables.

Examples 394-403



Example	Boronic acid	R
394	2-Ethoxyphenylboronic acid	
395	Pyrimidine-5-boronic acid	
396	Pyridine-3-boronic acid	
397	2-Methoxypyrimidine-5-boronic acid	
398	2-Methoxy-5-pyridineboronic acid	
399	4-Methoxy-3-pyridineboronic acid	
400	3-Methoxypyridine-5-boronic acid pinacol ester	
401	3-(Morpholine-4-carbonyl)phenylboronic acid	
402	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	

403	5-Ethoxymethylpyridin-3-ylboronic acid	

The characterization data for Examples 394-402 are shown in the table below.

Examples 394-403

Example	Name	Form	mp (°C)	Anal.
394	1-[4-Amino-7-(2-ethoxyphenyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White solid	173-175	Calcd for $C_{24}H_{28}N_4O_3$: C, 68.55; H, 6.71; N, 13.32. Found: C, 68.38; H, 6.92; N, 13.47.
395	1-[4-Amino-2-methoxymethyl-7-(pyrimidin-5-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White powder	220-220.5	Calcd for $C_{20}H_{22}N_6O_2$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.30; H, 5.72; N, 22.21.
396	1-[4-Amino-2-methoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White solid	225-225.5	Calcd for $C_{21}H_{23}N_5O_2$: C, 65.70; H, 6.23; N, 18.24. Found: C, 65.30; H, 5.57; N, 17.99.
397	1-[4-Amino-2-methoxymethyl-7-(2-methoxypyrimidin-5-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White solid	241-242	Calcd for $C_{21}H_{24}N_6O_3$: C, 59.17; H, 6.14; N, 19.71. Found: C, 59.33; H, 6.12; N, 19.73.

398	1-[4-Amino-2-methoxymethyl-7-(6-methoxypyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White powder	190-190.5	Calcd for $C_{22}H_{25}N_5O_3$: C, 64.85; H, 6.18; N, 17.19. Found: C, 64.61; H, 5.97; N, 17.13.
399	1-[4-Amino-2-methoxymethyl-7-(4-methoxypyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White powder	220.5-222	Calcd for $C_{22}H_{25}N_5O_3$: C, 64.85; H, 6.18; N, 17.19. Found: C, 64.54; H, 5.90; N, 17.11.
400	1-[4-Amino-2-methoxymethyl-7-(5-methoxypyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	Yellow powder	234-236	Calcd for $C_{22}H_{25}N_5O_3 \bullet 0.13$ CH_2Cl_2: C, 63.51; H, 6.08; N, 16.73. Found: C, 63.26; H, 5.83; N, 16.61.
401	{3-[4-Amino-1-(2-hydroxy-2-methylpropyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}morpholin-4-ylmethanone	White solid	176-177	Calcd for $C_{27}H_{31}N_5O_4 \bullet 1.0H_2O$: C, 63.89; H, 6.55; N, 13.80. Found: C, 63.50; H, 6.44; N, 13.64.
402	1-[4-Amino-7-(5-hydroxymethylpyridin-3-yl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	White powder	224-225	Calcd for $C_{22}H_{25}N_5O_3 \bullet 1.5H_2O$: C, 60.82; H, 6.50; N, 16.12. Found: C, 60.81; H, 6.51; N, 16.14.

Example 403

1-[4-Amino-7-(5-ethoxymethylpyridin-3-yl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

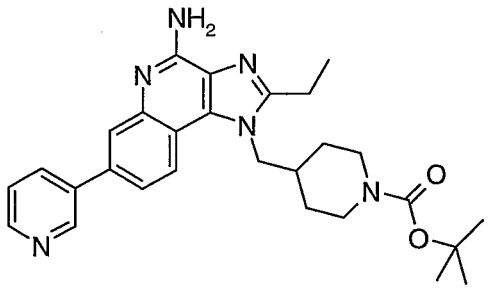
The product from the coupling reaction was further purified by recrystallizing twice from acetonitrile:isopropanol followed by a second chromatographic purification on silica gel (eluting with chloroform:CMA in a gradient from 99:1 to 70:30) to provide the product as a white powder.

^{1}H NMR (300mHz, DMSO-d_6 @ 45°C) δ 8.90 (d, J = 2.2 Hz, 1H), 8.54 (d, J = 1.9 Hz, 1H), 8.40 (d, J = 8.6 Hz, 1H), 8.07 (t, J = 2.1 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.57 (dd, J = 8.6, 2.0 Hz, 1H), 6.54 (br s, 2H), 4.89 (br s, 2H), 4.83 (br s, 1H), 4.69 (br s, 2H), 4.60 (br s, 2H), 3.58 (q, J = 7.0 Hz, 2H), 3.34 (s, 3H), 1.22-1.17 (m, 9H);

MS (ESI) *m/z* 436.2361 (436.2349 calcd for $C_{24}H_{29}N_5O_3$, M+H).

Example 404

tert-Butyl 4-{[4-amino-2-ethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate



Part A

The method described in Part A of Examples 142-144 was used to treat *tert*-butyl 4-[(3-amino-7-bromoquinolin-4-ylamino)methyl]piperidine-1-carboxylate (15.0 g, 34.5 mmol) with triethyl orthopropionate (6.68 g, 37.9 mmol). After completion, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluting with 95:5 chloroform:CMA) followed by recrystallization from ethyl acetate to provide 12.6 g of *tert*-butyl 4-[(7-bromo-2-ethyl-1*H*-imidazo[4,5-

c]quinolin-1-yl)methyl]piperidine-1-carboxylate as a white powder, mp 208-209 °C.

Anal. Calcd for $C_{23}H_{29}BrN_4O_2$: C, 58.35; H, 6.17; N, 11.83. Found: C, 58.13; H, 5.85; N, 11.69.

Part B

tert-Butyl 4-[(7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized; the amination reaction was stirred for 16 hours. The product from amination was purified by column chromatography on silica gel (eluting with 90:10 chloroform:CMA) followed by recrystallization from ethyl acetate to provide *tert*-butyl 4-[(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate as an off-white powder, mp 131-132 °C.

Anal. Calcd for $C_{23}H_{30}BrN_5O_2$: C, 56.56; H, 6.19; N, 14.34. Found: C, 56.30; H, 6.14; N, 14.06.

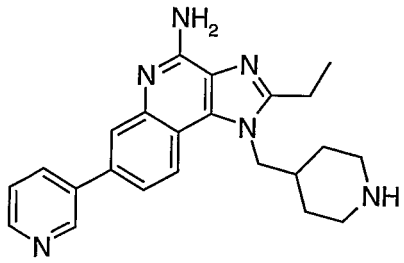
Part C

tert-Butyl 4-[(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate (9.24 g, 18.9 mmol) and pyridine-3-boronic acid 1,3-propanediol cyclic ester (3.39 g, 20.8 mmol) were coupled according to the method described in Examples 118-121. Additional reagents were added after the reaction was heated for 16 hours, and the reaction was continued for 16 hours. Water (20 mL) was added, and the *n*-propanol was removed under reduced pressure. The remaining mixture was extracted with chloroform (2 x 200 mL), and the combined organic fractions were purified by column chromatography on silica gel (eluting with chloroform and chloroform:CMA). The resulting solid was recrystallized from acetonitrile to provide 5.44 g of *tert*-butyl 4-{[4-amino-2-ethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate as a white, fluffy solid, mp 229-231 °C.

Anal. Calcd for $C_{28}H_{34}N_6O_2$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.18; H, 7.07; N, 17.36.

Example 405

2-Ethyl-1-(piperidin-4-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride



The method described in Example 177 was used to convert *tert*-butyl 4-{[4-amino-2-ethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate (5.22 g, 10.7 mmol) to 5.15 g of 2-ethyl-1-(piperidin-4-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride, which was obtained as a white solid, mp >250 °C.

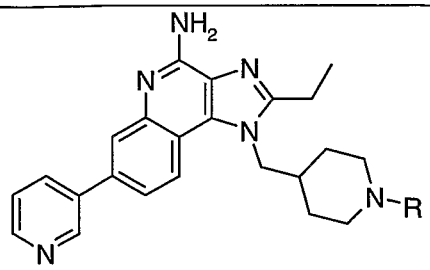
Anal. Calcd for $C_{23}H_{26}N_6 \cdot 3HCl \cdot 1.4\ H_2O$: C, 53.01; H, 6.15; N, 16.13. Found: C, 53.40; H, 6.53; N, 16.15.

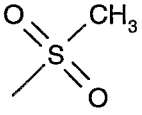
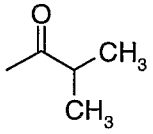
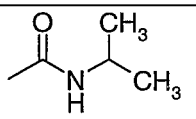
Examples 406-408

A solution of 2-ethyl-1-(piperidin-4-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride (1.50 g, 2.88 mmol) and triethylamine (5 or 10 equivalents) in chloroform (100 mL for Example 406 and 250 mL for Examples 407 and 408) and pyridine (60 mL for Example 406 and 100 mL for Examples 407 and 408) was cooled to 4 °C. The reagent from the table below (1 equivalent) was added dropwise, and the reaction was allowed to warm to ambient temperature and stirred for between 12 and 48 hours, with additional reagents added in Example 406. For Example 406, the reaction mixture was diluted with chloroform, and the resulting solution was washed sequentially with water (100 mL), 4% aqueous sodium carbonate (2 x 50 mL), water (50 mL), and brine (50 mL) and then concentrated under reduced pressure. For Examples 407 and 408, the reaction mixture was concentrated under reduced pressure and then triturated with 5 N aqueous sodium hydroxide to afford a solid that was isolated by filtration. The crude products were purified by flash column chromatography on silica gel (eluting with chloroform and chloroform:CMA) followed by recrystallization from acetonitrile to provide the products shown in

the table below. The following table contains characterization data for these compounds.

Examples 406-408



Example	Reagent	R
406	Methanesulfonyl chloride	
407	Isobutyryl chloride	
408	Isopropyl isocyanate	

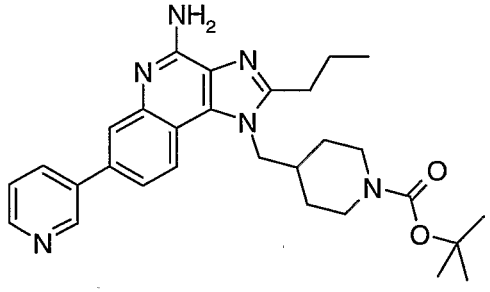
Examples 406-408

Example	Name	Form	mp (°C)	Anal.
406	2-Ethyl-1-{[1-(methanesulfonyl)piperidin-4-yl]methyl}-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White crystalline solid	228-229	Calcd for $C_{24}H_{28}N_6O_2S \cdot 0.86\ H_2O$: C, 60.04; H, 6.24; N, 17.50. Found: C, 60.21; H, 6.51; N, 17.43.

407	1-{4-[4-Amino-2-ethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl]piperidin-1-yl}-2-methylpropan-1-one	White crystalline solid	189-191	Calcd for $C_{27}H_{32}N_6O \cdot 0.5 H_2O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.58; H, 7.26; N, 18.11.
408	4-[4-Amino-2-ethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl]piperidin-1-carboxylic acid isopropylamide	White solid	255-256	Calcd for $C_{27}H_{33}N_7O \cdot 1.25 H_2O$: C, 65.63; H, 7.24; N, 19.84. Found: C, 65.58; H, 7.03; N, 19.85.

Example 409

tert-Butyl 4-{[4-amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate



Part A

The method described in Part A of Examples 142-144 was used to treat *tert*-butyl 4-[(3-amino-7-bromoquinolin-4-ylamino)methyl]piperidine-1-carboxylate (15.0 g, 34.5 mmol) with trimethyl orthobutyrate (5.62 g, 37.9 mmol). After completion, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluting with 95:5 chloroform:CMA) followed by recrystallization from ethyl acetate to provide 13.1 g of *tert*-butyl 4-[(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate as a white solid, mp 215-216 °C.

Anal. Calcd for $C_{24}H_{31}BrN_4O_2$: C, 59.14; H, 6.41; N, 11.49. Found: C, 59.06; H, 6.24; N, 11.42.

Part B

tert-Butyl 4-[(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized; the amination reaction was stirred for 16 hours. The product from amination was purified by column chromatography on silica gel (eluting with 90:10 chloroform:CMA) followed by recrystallization from ethyl acetate to provide *tert*-butyl 4-[(4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate as off-white needles, mp 134-137 °C..

Anal. Calcd for $C_{24}H_{32}BrN_5O_2$: C, 57.37; H, 6.42; N, 13.94. Found: C, 57.14; H, 6.41; N, 13.52.

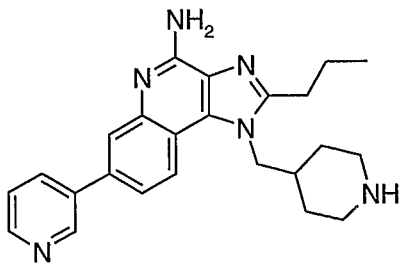
Part C

tert-Butyl 4-[(4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate (8.02 g, 15.9 mmol) and pyridine-3-boronic acid 1,3-propanediol cyclic ester (2.86 g, 17.6 mmol) were coupled according to the method described in Part C of Example 404 to provide, after purification, 4.12 g of *tert*-butyl 4-{[4-amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate as an off-white solid, mp 209-211 °C.

Anal. Calcd for $C_{29}H_{36}N_6O_2 \cdot 0.6\ H_2O$: C, 68.10; H, 7.33; N, 16.43. Found: C, 67.72; H, 7.26; N, 16.31.

Example 410

1-(Piperidin-4-ylmethyl)-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride

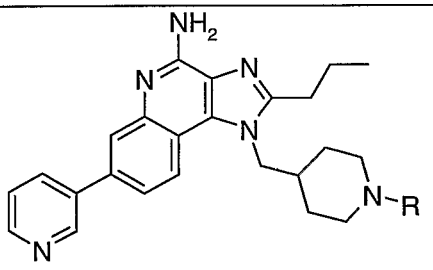


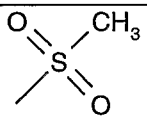
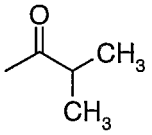
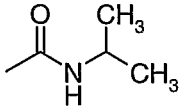
The method described in Example 177 was used to convert *tert*-butyl 4-{[4-amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate (4.00 g, 7.99 mmol) to 3.84 g of 1-(piperidin-4-ylmethyl)-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride, which was obtained as a white solid, mp >250 °C. Anal. Calcd for $C_{24}H_{28}N_6 \cdot 3HCl \cdot 0.59\ H_2O$: C, 55.39; H, 6.23; N, 16.15. Found: C, 55.35; H, 6.52; N, 16.08.

Examples 411-413

The methods described for Examples 406, 407, and 408 were carried out for Examples 411, 412, and 413 respectively to provide the products shown in the table below.

Examples 411-413



Example	Reagent	R
411	Methanesulfonyl chloride	
412	Isobutyryl chloride	
413	Isopropyl isocyanate	

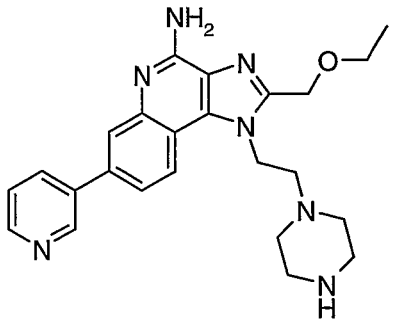
Characterization data for Examples 411-413 are shown in the table below.

Examples 411-413

Example	Name	Form	mp (°C)	Anal.
411	1-{[1-(Methanesulfonyl)piperidin-4-yl]methyl}-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	>250	Calcd for $C_{25}H_{30}N_6O_2S$•0.8 HCl•1.0 H_2O: C, 57.11; H, 6.29; N, 15.98; Cl, 5.39. Found: C, 56.87; H, 6.68; N, 15.77; Cl, 5.02.
412	1-{4-[4-Amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl]piperidin-1-yl}-2-methylpropan-1-one	White solid	248-249	Calcd for $C_{28}H_{34}N_6O$: C, 71.46; H, 7.28; N, 17.86. Found: C, 71.21; H, 7.33; N, 17.55.
413	4-[4-Amino-2-ethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl]piperidin-1-carboxylic acid isopropylamide	Off-white solid	240-242	Calcd for $C_{28}H_{35}N_7O$: C, 69.25; H, 7.26; N, 20.19. Found: C, 68.98; H, 7.20; N, 20.35.

Example 414

2-Ethoxymethyl-1-(2-piperazin-1-ylethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

7-Bromo-4-chloro-3-nitroquinoline (33.0 g, 115 mmol) was treated with 4-(2-aminoethyl)-1-(*tert*-butoxycarbonyl)piperazine (26.4 mL, 115 mmol) according to the method described in Part E of Example 1. The reaction was stirred overnight. The crude product was triturated with diethyl ether and isolated by filtration to provide 33.05 g of *tert*-butyl 4-[2-(7-bromo-3-nitroquinolin-4-ylamino)ethyl]piperazine-1-carboxylate as a yellow solid.

Part B

tert-Butyl 4-[2-(7-bromo-3-nitroquinolin-4-ylamino)ethyl]piperazine-1-carboxylate was treated according to the methods described in Parts B through D of Examples 152-156. Triethylamine (1.1 equivalents) was added to the reaction in Part C, and the reaction in Part D was heated at reflux overnight. Following chromatographic purification in Part D (eluting with chloroform:CMA in a gradient from 100:0 to 94:6), *tert*-butyl 4-[2-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]piperazine-1-carboxylate was obtained as a white solid, mp 140-143 °C.

Anal. Calcd for $C_{24}H_{32}BrN_5O_3$: C, 55.60; H, 6.22; N, 13.51. Found: C, 55.62; H, 6.31; N, 13.40.

Part C

tert-Butyl 4-[2-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]piperazine-1-carboxylate (21.5 g, 41.5 mmol) was oxidized with three equivalents of 3-chloroperoxybenzoic acid (28.63 g of 75% pure material, 124.4 mmol) according to the method described Part H of Example 1 to provide *tert*-

butyl 4-[2-(7-bromo-2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-4-oxidopiperazine-1-carboxylate, which was used without purification.

Part D

tert-Butyl 4-[2-(7-bromo-2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-4-oxidopiperazine-1-carboxylate was aminated according to the method described in Part I of Example 1. The reaction was stirred overnight, and the crude product was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 70:30) to provide 10.84 g of *tert*-butyl 4-[2-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-4-oxidopiperazine-1-carboxylate as a white solid.

Part E

A solution of *tert*-butyl 4-[2-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-4-oxidopiperazine-1-carboxylate (8.84 g, 16.1 mmol) in chloroform (400 mL) was cooled to 4 °C. Phosphorous trichloride (9.82 mL, 113 mmol) was added dropwise, and the reaction was stirred for 45 minutes at 4 °C. Water (one drop) was added to the reaction, which was allowed to warm to ambient temperature. The chloroform was removed under reduced pressure, and the residue was dissolved in ethanol (150 mL). Hydrogen chloride (21.5 mL of a 3 M solution in ethanol) was added, and the reaction was heated at reflux for 25 minutes. The reaction was allowed to cool to room temperature; a precipitate formed and was isolated by filtration to provide 6.86 g of 7-bromo-2-ethoxymethyl-1-(2-piperazin-1-ylethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride as a light yellow solid.

Part F

Under a nitrogen atmosphere, triphenylphosphine (0.0409 g, 0.156 mmol), 2 M aqueous sodium carbonate (18.3 mL, 36.5 mmol) and a solution of palladium (II) acetate (0.0117 g, 0.52 mmol) in warm toluene were added to a solution of 7-bromo-2-ethoxymethyl-1-(2-piperazin-1-ylethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride (5.28 g, 10.4 mmol) and pyridine-3-boronic acid 1,3-propanediol cyclic ester (1.87 g, 11.5 mmol) in *n*-propanol (8 mL). The reaction was heated at reflux under nitrogen for three hours then allowed to cool

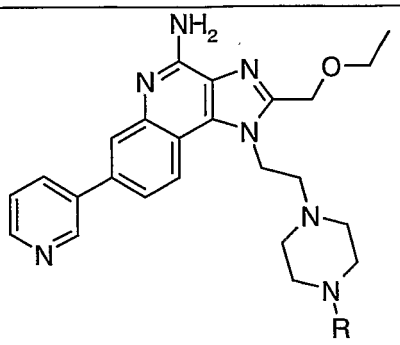
to ambient temperature. Deionized water was added, and organic solvent was removed under reduced pressure. The aqueous mixture was extracted with ethyl acetate (3 x), and the combined organic fractions were washed sequentially with 2 M aqueous sodium carbonate and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was combined with material from another run and purified by flash column chromatography on silica gel (eluting with chloroform:methanol in a gradient from 90:10 to 50:50 and 50:50 chloroform:CMA) to provide 3.54 g of 2-ethoxymethyl-1-(2-piperazin-1-ylethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 208-211 °C.

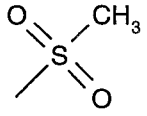
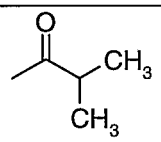
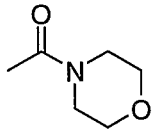
Anal. Calcd for $C_{24}H_{29}N_7O \cdot 0.5\ H_2O$: C, 65.43; H, 6.86; N, 22.26. Found: C, 65.59; H, 7.09; N, 22.53.

Examples 415-417

A 0.015 M solution of 2-ethoxymethyl-1-(2-piperazin-1-ylethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.00 g, 2.32 mmol) and triethylamine (1.3-1.4 equivalents) in chloroform was cooled to 4 °C. The reagent from the table below (1.1-1.2 equivalents) was added dropwise, and the reaction was allowed to warm to ambient temperature and stirred for two or three hours. In Examples 415 and 417, additional triethylamine and the reagent indicated in the table were added at 4 °C, and the reaction was stirred overnight. The work-up procedure described in Examples 178 to 181 was carried out. The crude product was purified by flash column chromatography on silica gel or by HPFC (eluting with chloroform:CMA in a gradient from about 100:0 to 75:25) followed by recrystallization from acetonitrile to provide the products shown in the table below.

Examples 415-417



Example	Reagent	R
415	Methanesulfonyl chloride	
416	Isobutyryl chloride	
417	4-Morpholinecarbonyl chloride	

The characterization data for Examples 415-417 are provided in the table below.

Examples 415-417

Example	Name	Form	mp (°C)	Anal.
415	2-Ethoxymethyl-1-{2-[4-(methanesulfonyl)piperazin-1-yl]ethyl}-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	205-207	Calcd for $C_{25}H_{31}N_7O_3S \cdot 0.65\ H_2O$: C, 57.60; H, 6.25; N, 18.81. Found: C, 57.51; H, 6.22; N, 18.79.

416	1-(4-{2-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}piperazin-1-yl)-2-methylpropan-1-one	White solid	190-192	Calcd for $C_{28}H_{35}N_7O_2 \cdot 0.5$ H_2O: C, 65.86; H, 7.11; N, 19.20. Found: C, 65.90; H, 7.07; N, 19.34.
417	1-(4-{2-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}piperazin-1-yl)morpholin-4-ylmethanone	Light yellow solid	212-214	$C_{29}H_{36}N_8O_3 \cdot 0.5$ H_2O: C, 62.91; H, 6.74; N, 20.24. Found: C, 63.02; H, 6.69; N, 20.26.

Examples 418-420

Part A

Trimethyl orthobutyrate (11.61 mL, 72.6 mmol) and catalytic pyridine hydrochloride were added to a solution of 1-(3-amino-7-bromoquinolin-4-ylamino)-2-methylpropan-2-ol (22.51 g, 72.6 mmol) in anhydrous toluene (120 mL), and the reaction was heated at reflux for two hours. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane and washed with water. The dichloromethane was removed under reduced pressure until a precipitate began to form. Hexanes were added, and the precipitate was isolated by filtration to provide 20.17 g of 1-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol.

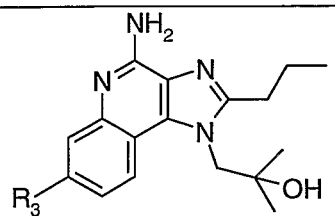
Part B

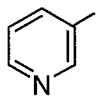
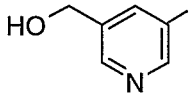
1-(7-Bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol was oxidized and then aminated according to the methods described in Part E of Examples 125-135 to provide 14.6 g of 1-(4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as a white solid, which was used without purification.

Part C

1-(4-Amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol and the boronic acid from the table below were coupled according to the general procedure described in Part J of Example 1. Example 420 was heated at reflux overnight. The purification and characterization of each compound is described below the table.

Examples 418-420



Example	Boronic acid or ester	R_3
418	Pyridine-3-boronic acid	
419	Phenylboronic acid	
420	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	

Example 418

1-[4-Amino-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The reaction mixture was concentrated under reduced pressure, and hexanes were added to form a precipitate. The precipitate was isolated by filtration and purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) to provide the product as an off-white solid, mp 238.5-241°C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.57 (d, J = 3.6 Hz, 1H), 8.38 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.9 (s, 1H), 7.55-7.47 (m, 2H), 6.39 (s,

2H), 4.71 (s, 1H), 4.56 (br s, 2H), 3.01 (t, J = 7.2 Hz, 2H), 1.86 (sextet, J = 7.5 Hz, 2H), 1.2 (s, 6H), 1.01 (t, J = 7.5 Hz, 3H);

MS (APCI) m/z 376 $(M + H)^+$;

Anal. Calcd for $C_{22}H_{25}N_5O \cdot 0.33\ H_2O$: C, 69.28; H, 6.78; N, 18.36. Found: C, 69.68; H, 7.24; N, 18.58.

Example 419

1-[4-Amino-7-phenyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The isolated solid was recrystallized from methanol:water and then purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30). A second recrystallization was carried out with acetonitrile:isopropanol to provide the product as a white solid.

^{1}H NMR (300mHz, DMSO-d_6) δ 8.35 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.77-7.74 (m, 2H), 7.52-7.47 (m, 3H), 7.39-7.34 (m, 1H), 6.32 (br s, 2H), 4.71 (s, 1H), 4.57 (br s, 2H), 3.02 (t, J = 7.4 Hz, 2H), 1.86 (sextet, J = 7.6 Hz, 2H), 1.21 (br s, 6H), 1.02 (t, J = 7.3 Hz, 3H);

MS (ESI) 375.2180 (375.2185 calcd for $C_{23}H_{26}N_4O$).

Example 420

1-[4-Amino-7-(5-hydroxymethylpyridin-3-yl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol

The crude product was purified by HPFC (eluting with ethyl acetate and then chloroform:CMA in a gradient from 90:10 to 70:30) and then deprotected according to the method described in Part C of Example 150. The product from the deprotection was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 60:40). The resulting product was mixed with dichloromethane and concentrated under reduced pressure until a solid began to form. The solid was isolated by filtration and dried under vacuum to provide 1-[4-amino-7-(5-hydroxymethylpyridin-3-yl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white solid, mp 225 - 226 °C.

Anal. Calcd for $C_{23}H_{27}N_5O_2 \cdot 0.67\ H_2O$: C, 66.17; H, 6.84; N, 16.78. Found: C, 65.86; H, 6.85; N, 16.66.

Example 421-424

Part A

The method described in Part A of Example 200 was used to treat 7-bromo-4-chloro-3-nitroquinoline (50.0 g, 174 mmol) with 1,2-diamino-2-methylpropane (36.5 mL, 348 mmol) and triethylamine (45 mL, 260 mmol). Following the work-up procedure, the solution of N^1-(3-nitro-7-bromoquinolin-4-yl)-2-methylpropane-1,2-diamine in dichloromethane was concentrated to a volume of 1L.

Part B

The solution from Part A was cooled to 0 °C under a nitrogen atmosphere. Triethylamine (48.5 mL, 348 mmol) was added followed by a solution of di-*tert*-butyl dicarbonate (41.8 g, 191 mmol) in dichloromethane (200 mL) over a period of 30 minutes. The reaction was allowed to warm to ambient temperature and stirred for three days. The reaction was washed with deionized water (2 x 500 mL) and brine (500 mL), dried over sodium sulfate and magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure to provide 58 g of *tert*-butyl [2-(7-bromo-3-nitroquinolin-4-ylamino)-1,1-dimethylethyl]carbamate as a yellow solid.

Part C

The method described in Part B of Examples 125-135 was used to reduce *tert*-butyl [2-(7-bromo-3-nitroquinolin-4-ylamino)-1,1-dimethylethyl]carbamate (58.05 g, 132 mmol) to 23.74 g of *tert*-butyl [2-(3-amino-7-bromoquinolin-4-ylamino)-1,1-dimethylethyl]carbamate as an orange solid.

Part D

A modification of the method described in Part C of Examples 125-135 was used to treat *tert*-butyl [2-(3-amino-7-bromoquinolin-4-ylamino)-1,1-dimethylethyl]carbamate (23.7 g, 58.0 mmol) with ethoxyacetyl chloride (6.4 mL, 58 mmol). Triethylamine (12.1 mL, 87.0 mmol) was added to the reaction, which was stirred overnight. The reaction was washed with deionized water (2x) and brine, dried over sodium sulfate and magnesium sulfate, filtered, and concentrated under reduced pressure to provide 26.25 g of an orange solid.

Part E

The method described in Part D of Examples 152-156 was followed. The reaction was heated at reflux for four days. The crude product was purified first by HPFC (eluting with chloroform:CMA in a gradient from 85:15 to 80:20) and then by column chromatography on silica gel (eluting with 85:15 chloroform:CMA) to provide 15.94 g of *tert*-butyl [2-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]carbamate as a brown solid.

Part F

tert-Butyl [2-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]carbamate (15.94 g, 33.39 mmol) was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation reaction was carried out in chloroform and stirred overnight. The product was not recrystallized. The product from amination, *tert*-butyl [2-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]carbamate, was obtained as a brown solid after the work-up procedure and used without purification.

Part G

The material from Part F was deprotected according to the method described in Example 177. The work-up procedure described in Example 192 was followed with the exception that the aqueous solution was washed with twice dichloromethane before ammonium hydroxide was added. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 95:5 to 90:10) to provide 7.27 g of 1-(2-amino-2-methylpropyl)-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan solid.

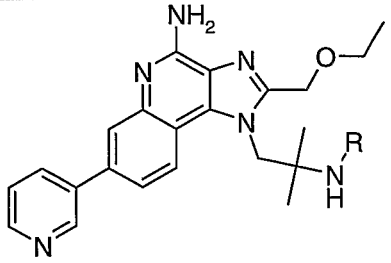
Part H

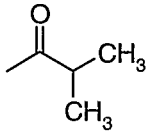
A solution of 1-(2-amino-2-methylpropyl)-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1equivalent, 4.5-5 mmol) in the solvent shown in the table below was cooled to -20 °C or 0 °C; triethylamine (2 equivalents) was added. The reagent shown in the table below (1.1 equivalents) was added slowly, and the reaction was stirred for between one hour and overnight. The reaction was washed with deionized water (2x) and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product

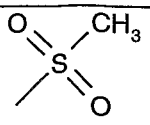
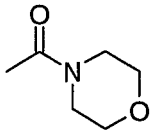
was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30 for Examples 422 and 424 and with 90:10 dichloromethane:methanol for Example 423).

Part I

Under a nitrogen atmosphere, triphenylphosphine (0.015 equivalents), 2 M aqueous sodium carbonate (1.2 equivalents) and a solution of palladium (II) acetate in warm toluene (0.005 equivalents) were added to a solution of the material from Part G (Example 421) or Part H (Examples 422-424) (1 equivalent) and pyridine-3-boronic acid 1,3-propanediol cyclic ester (1.1 equivalents) in *n*-propanol (0.05-0.15 M). The reaction was heated at reflux under nitrogen for 1.5 to 3.5 hours. Deionized water was added, and organic solvent was removed under reduced pressure. The aqueous mixture was extracted twice with ethyl acetate, and the combined organic fractions were washed with 2 M aqueous sodium carbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) to provide the product shown in the table below. Characterization data are shown after the table.



Example	Solvent for Part H (concentration)	Reagent for Part H	R
421	Not used	Not used	H
422	NMP (0.17 M)	Isobutyryl chloride	

423	Dichloromethane (0.1 M)	Methanesulfonic anhydride	
424	Dichloromethane (0.1 M)	4-Morpholinecarbonyl chloride	

Example 421

1-(2-Amino-2-methylpropyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

The product was obtained as an off-white powder. Anal. Calcd for $C_{22}H_{26}N_6O \cdot 0.25\ H_2O$: C, 66.90; H, 6.76; N, 21.28. Found: C, 66.62; H, 7.05, N, 21.34.

Example 422

N-{2-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}-2-methylpropamide

The product was obtained as a yellow powder. Anal. Calcd for $C_{26}H_{32}N_6O_2 \cdot 0.40\ H_2O$: C, 67.02; H, 7.05; N, 18.04. Found: C, 66.81; H, 7.25, N, 18.06.

Example 423

N-{2-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide

The product was obtained as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (d, J = 1.8 Hz, 1H), 8.59 (dd, J = 4.7, 1.5 Hz, 1H), 8.41 (d, J = 8.6 Hz, 1H), 8.19 (m, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.59-7.50 (m, 2H), 7.33 (s, 1H), 6.73 (s, 2H), 4.90 (s, 4H), 3.57 (q, J = 7.0 Hz, 2H), 3.01 (s, 3H), 1.32 (br s, 6H), 1.15 (t, J = 7.0 Hz, 3H); MS (ESI) *m/z* 469.2018 (469.2022 calcd for $C_{23}H_{28}N_6O_3S$, M + H^+).

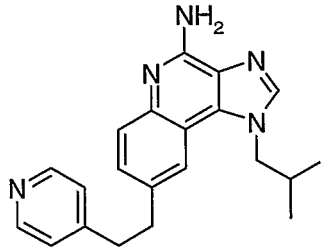
Example 424

N-{2-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}morpholine-4-carboxamide

The product was obtained as an off-white powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (d, J = 2.1 Hz, 1H), 8.62 (m, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.06-8.01 (m, 2H), 7.57 (m, 1H), 7.41 (m, 1H), 5.49 (s, 2H), 5.14 (s, 2H), 4.82 (br s, 2H), 4.44 (s, 1H), 3.62 (m, 6H), 3.22 (m, 4H), 1.41 (br s, 6H), 1.26 (m, 3H); MS (ESI) *m/z* 504.2734 (504.2723 calcd for $C_{27}H_{33}N_7O_3$, M + H^+).

Example 425

1-(2-Methylpropyl)-8-(2-pyridin-4-ylethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (30.0 g, 125 mmol) in chloroform (620 mL) was heated to 50 °C, and *N*-bromosuccinimide (28.8 g, 162 mmol) was added in five portions over a period of five minutes. The resulting dark red solution was heated at reflux for 45 minutes, allowed to cool to ambient temperature, and stirred for one hour. A precipitate formed, was isolated by filtration, and was washed with water and diethyl ether to provide 9.0 g of 8-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]-quinolin-4-amine as a solid.

Part B

Nitrogen was bubbled through a solution of 8-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]-quinolin-4-amine (3.0 g, 9.4 mmol), 4-vinylpyridine (2.0 mL, 19 mmol), triphenylphosphine (246 mg, 0.94 mmol), and triethylamine (2.7 mL, 19 mmol) in acetonitrile (50 mL) for 15 minutes. Palladium (II) acetate (105 mg, 0.47 mmol) was added, and the reaction was heated at 100 °C for three days. The solvent was removed under reduced

pressure, and the residue was adjusted to pH 2 with the addition of concentrated hydrochloric acid. Water was added, and the mixture was filtered through a layer of CELITE filter aid. Aqueous sodium carbonate (2 N) was added to the filtrate to adjust the solution to pH 10. The solution was then extracted with dichloromethane, and the combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 80:20) to provide 2.1 g of 1-(2-methylpropyl)-8-(2-pyridin-4-ylvinyl)-1*H*-imidazo[4,5-*c*]-quinolin-4-amine as a yellow solid.

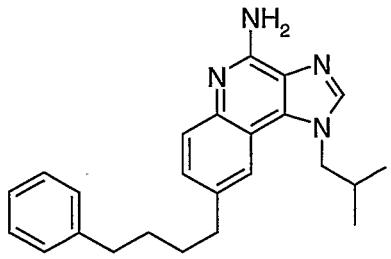
Part C

1-(2-Methylpropyl)-8-(2-pyridin-4-ylvinyl)-1*H*-imidazo[4,5-*c*]-quinolin-4-amine (2.1 g, 6.1 mmol) was treated according to the method described in Example 123; the reaction was allowed to run for seven days. An analysis by proton nuclear magnetic resonance spectroscopy indicated the presence of starting material in the purified product. The product mixture was dissolved in methanol (100 mL), and 10% palladium on carbon (200 mg) was added. The reaction was placed under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) for four days, and the product was isolated as described in Example 123. The crude product was purified by flash column chromatography on silica gel (eluting with 90:10 chloroform:CMA) followed by recrystallization from acetonitrile to provide 380 mg of 1-(2-methylpropyl)-8-(2-pyridin-4-ylethyl)-1*H*-imidazo[4,5-*c*]-quinolin-4-amine as pale, yellow crystals, mp 221-224 °C.

Anal. Calcd for $C_{21}H_{23}N_5$: C, 73.02; H, 6.71; N, 20.27. Found: C, 72.77; H, 6.39; N, 20.23.

Example 426

1-(2-Methylpropyl)-8-(4-phenylbutyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

8-Bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3.0 g, 9.4 mmol) was treated with 4-phenyl butene (4.2 mL, 28.2 mmol) according to the method described in Part B of Example 425. The reaction was heated overnight. Following chromatographic purification (eluting with 95:5 chloroform:methanol), 1.8 g of 1-(2-methylpropyl)-8-(4-phenylbut-1-enyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine were obtained as an off-white solid.

Part B

1-(2-Methylpropyl)-8-(4-phenylbut-1-enyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.8 g, 4.8 mmol) was treated according to the method described in Example 123. The crude product was recrystallized from acetonitrile and then from methanol to provide 700 mg of 1-(2-methylpropyl)-8-(4-phenylbutyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as white crystals, mp 176-177 °C.

Anal. Calcd for $C_{24}H_{28}N_4$: C, 77.38; H, 7.58; N, 15.04. Found: C, 76.99; H, 7.45; N, 14.97.

Examples 427-429

Part A

A solution of (7-bromo-3-nitroquinolin-4-yl)-(2-methylpropyl)amine (30.9 g, 105 mmol) in acetonitrile (1.8 L) and isopropanol (200 mL) was added to a Parr vessel. A mixture of 5% platinum on carbon (3.0 g) and acetonitrile:isopropanol (20 mL) was added, and the vessel was purged with nitrogen. The vessel was placed under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) for two hours. After one hour, the pressure had decreased to 20 psi (1.4 x 10^5 Pa) and was readjusted to 40 psi (2.8 x 10^5 Pa). The reaction mixture was

filtered through a layer of CELITE filter aid, and the filter cake was washed with acetonitrile. The filtrate was concentrated under reduced pressure to provide 7-bromo-N^4-(2-methylpropyl)quinoline-3,4-diamine as an oil.

Part B

Under a nitrogen atmosphere, a mixture of the material from Part A, triethyl orthoformate (20.9 mL, 126 mmol), and pyridine hydrochloride (3.1 g, 27 mmol) in acetonitrile was heated at reflux for 20 minutes. A Dean-Stark trap was used to collect the volatiles. The reaction mixture was concentrated under reduced pressure to provide 18.7 g of 7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline as a gold solid.

Part C

The method described in Part J of Example 365 was used to oxidize and aminate 7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (18.7 g, 58.4 mmol). 3-Chloroperoxybenzoic acid (22.1 g of 50% pure material, 129 mmol) was added in five portions during the oxidation step, and the amination with ammonium hydroxide (146 mL) and *p*-toluenesulfonyl chloride (16.6 g, 87.6 mmol) proceeded overnight. The crude product was obtained as an oil, which was treated with acetonitrile to form a precipitate. The precipitate was isolated by filtration, washed with a small amount of acetonitrile, and recrystallized from acetonitrile to provide 4 g of 7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as off-white needeles, mp 218-220 °C.

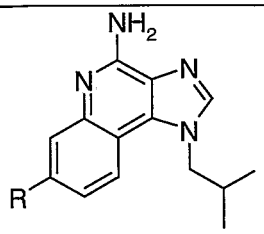
Anal. Calcd for $C_{14}H_{15}BrN_4$: C, 52.68; H, 4.74; N, 17.55. Found: C, 52.55; H, 4.99; N, 17.44.

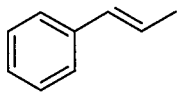
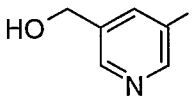
Part D

7-Bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine and the boronic acid indicated in the table below were coupled according to the general methods described in Part J of Example 1 and Part F of Examples 125-135. Palladium (II) acetate was added as a 5 mg/mL solution in toluene, and the reaction was heated overnight. The crude product was purified by flash column chromatography on silica gel (eluting with 90:10 chloroform:CMA for Examples 428 and 429 and chloroform:methanol in a gradient from 95:5 to 90:10 for

Example 427). Examples 427 and 428 were recrystallized from the solvents shown in the table below, isolated by filtration, and dried under high vacuum.

Example 429 was dissolved in THF (20 mL), and tetrabutylammonium fluoride (4.0 mL of a 1.0 M solution in THF) was added. The reaction was stirred for 15 minutes and concentrated under reduced pressure. The resulting black oil was purified by flash column chromatography on silica gel (eluting with methanol:CMA in a gradient from 90:10 to 75:25) to provide an oil that was stirred with acetonitrile at 0 °C to provide a solid, which was recrystallized from acetonitrile/methanol to provide the compound shown in the following table.



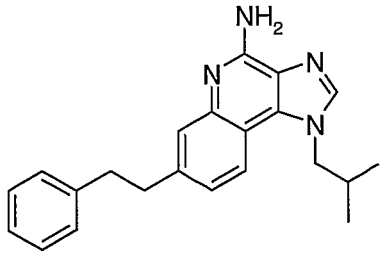
Example	Boronic Acid	Recrystallization solvent(s)	R
427	*trans*-2-Phenylvinylboronic acid	Methanol	
428	3-Pyridine boronic acid	Acetonitrile	
429	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	Acetonitrile/methanol	

Examples 427-429

Example	Name	Form	mp (°C)	Anal.
427	1-(2-Methylpropyl)-7-styryl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Light brown needles	257-258	Calcd for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36. Found: C, 76.86; H, 6.40; N, 16.44.
428	1-(2-Methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Gray needles	125	Calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07. Found: C, 70.99; H, 6.20; N, 21.88.
429	1-(2-Methylpropyl)-7-(5-hydroxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Yellow crystals	210-211	Calcd for $C_{20}H_{21}N_5O$: C, 69.14; H, 6.09; N, 20.16. Found: C, 68.96; H, 6.26; N, 20.22.

Example 430

1-(2-Methylpropyl)-7-phenethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



A modification of the method described in Example 123 was used to reduce 1-(2-methylpropyl)-7-styryl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.2 g, 3.5 mmol). The reaction was carried out in methanol (100 mL) for seven days. The crude product was purified by flash column chromatography on silica gel (eluting with 90:10 chloroform:CMA) followed by recrystallization from

acetonitrile to provide 1-(2-methylpropyl)-7-phenethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as white crystals, mp 172-173 °C.

Anal. Calcd for $C_{22}H_{24}N_4$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.56; H, 7.15; N, 16.24.

Examples 431-436

Part A

Triethyl orthoformate (10.0 mL, 60.1 mmol), Meldrum's acid (8.2 g, 57 mmol), and either 3-benzyl aniline or 4-benzyl aniline (10.0 g, 54.6 mmol) as indicated in the table below in methanol (303 mL) were combined and treated according to the method described in Part A of Example 1 to provide 5-[(3-benzylphenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (15.5 g) or 5-[(4-benzylphenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (15.2 g), respectively.

Part B

5-[(3-Benzylphenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (15.5 g, 46.0 mmol, Examples 431-433) or 5-[(4-benzylphenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (15.2 g, 45.0 mmol, Examples 434-436) was heated at 230 °C in DOWTHERM A heat transfer fluid for one hour, and then the reaction was allowed to cool to ambient temperature overnight.

For Examples 431-433, a 4.0 M solution of hydrogen chloride in 1,4-dioxane followed by diethyl ether were added to the reaction to precipitate a salt, which adhered to the sides of the reaction flask. The salt was washed with diethyl ether (3 x) and dissolved in dichloromethane. Sodium carbonate (2 M) was added to adjust the solution to pH 11, and water was added. The aqueous layer was separated and extracted with dichloromethane, and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by HPFC (eluting with chloroform:CMA in a gradient from 97:3 to 40:60) to provide 4.0 g of 7-benzylquinolin-4-ol and 4.75 g of 5-benzylquinolin-4-ol.

For Examples 434-436, a precipitate formed upon cooling and was isolated by filtration and washed with diethyl ether to provide 6-benzylquinolin-4-ol as a light brown solid.

Part C

The method described in Part D of Example 10 was used to treat 7-benzylquinolin-4-ol or 6-benzylquinolin-4-ol with nitric acid to provide 7-benzyl-3-nitroquinolin-4-ol or 6-benzyl-3-nitroquinolin-4-ol, respectively, as solids.

Part D

The method described in Part E of Example 10 was used to treat 7-benzyl-3-nitroquinolin-4-ol or 6-benzyl-3-nitroquinolin-4-ol with phosphorous oxychloride to provide 7-benzyl-4-chloro-3-nitroquinoline as a light yellow powder or 6-benzyl-4-chloro-3-nitroquinoline as a tan powder, respectively.

Part E

Under a nitrogen atmosphere, 1-amino-2-methylpropan-2-ol (1.2 equivalents) was added to a 0.2 M solution of 7-benzyl-4-chloro-3-nitroquinoline or 6-benzyl-4-chloro-3-nitroquinoline (1 equivalent) and triethylamine (3 equivalents) in dichloromethane, and the reaction was stirred overnight at ambient temperature. The volatiles were removed under reduced pressure, and the residue was stirred with water (50 mL) for one hour. The resulting yellow solid was isolated by filtration and washed with water to provide 1-(7-benzyl-3-nitroquinolin-4-ylamino)-2-methylpropan-2-ol or 1-(6-benzyl-3-nitroquinolin-4-ylamino)-2-methylpropan-2-ol, respectively.

Part F

A modification of the method described in Part A of Examples 427-429 was used to reduce 1-(7-benzyl-3-nitroquinolin-4-ylamino)-2-methylpropan-2-ol or 1-(6-benzyl-3-nitroquinolin-4-ylamino)-2-methylpropan-2-ol. The reaction was shaken for one or two days to provide 1-(3-amino-7-benzylquinolin-4-ylamino)-2-methylpropan-2-ol or 1-(3-amino-6-benzylquinolin-4-ylamino)-2-methylpropan-2-ol.

Part G

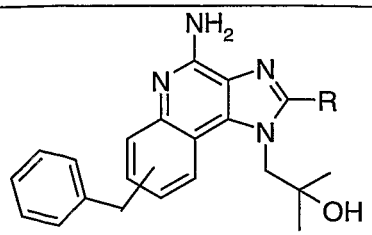
For Examples 431 and 434, a modification of the method described in Part B of Examples 427-429 was used to treat 1-(3-amino-7-benzylquinolin-4-ylamino)-2-methylpropan-2-ol or 1-(3-amino-6-benzylquinolin-4-ylamino)-2-methylpropan-2-ol with triethyl orthoformate, as indicated in the table below. The reaction was heated at reflux for one hour and then stirred overnight at ambient temperature. A precipitate formed, which was isolated by filtration to provide 1-(7-benzyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol or 1-(8-benzyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol.

For Examples 432, 433, 435, and 436, 1-(3-amino-7-benzylquinolin-4-ylamino)-2-methylpropan-2-ol or 1-(3-amino-6-benzylquinolin-4-ylamino)-2-methylpropan-2-ol was treated with the acid chloride shown in the table below according to the method described in Part A of Example 9. The reaction was heated overnight, and after the work-up procedure, the crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 99:1 to 70:30).

Part H

The method described in Part J of Example 365 was used to oxidize and aminate the material from Part G. 3-Chloroperoxybenzoic acid (1-1.5 equivalents of 50% pure material) was added in two portions over a period of 30 minutes during the oxidation step. After the work-up procedure, the crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from about 100:0 to about 60:40) followed by recrystallization from acetonitrile to provide the product shown in the table below. For Example 434, no chromatographic purification was carried out, and the product was recrystallized from acetonitrile:methanol.

Examples 431-436



Ex.	Starting material	Reagent in Part G	Product	R
431	3-Benzyl aniline	Triethyl orthoformate	7-Benzyl	-H
432	3-Benzyl aniline	Butyryl chloride	7-Benzyl	$-CH_2CH_2CH_3$
433	3-Benzyl aniline	Ethoxyacetyl chloride	7-Benzyl	$-CH_2OCH_2CH_3$
434	4-Benzyl aniline	Triethyl orthoformate	8-Benzyl	-H
435	4-Benzyl aniline	Butyryl chloride	8-Benzyl	$-CH_2CH_2CH_3$
436	4-Benzyl aniline	Ethoxyacetyl chloride	8-Benzyl	$-CH_2OCH_2CH_3$

Examples 431-436

Example	Name	Form	mp (°C)	Anal.
431	1-(4-Amino-7-benzyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	Brown crystals	228-229	Calcd for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.66; H, 6.37; N, 16.14.
432	1-(4-Amino-7-benzyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	Tan crystals	130-131	Calcd for $C_{24}H_{28}N_4O \cdot 0.25\ H_2O$: C, 73.35; H, 7.31; N, 14.26. Found: C, 73.04; H, 7.46; N, 14.30.

433	1-(4-Amino-7-benzyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	Light brown crystals	166-167	Calcd for $C_{24}H_{28}N_4O_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.92; H, 7.30; N, 14.05.
434	1-(4-Amino-8-benzyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	Pale yellow crystals	256-257	Calcd for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.56; H, 6.21; N, 16.13.
435	1-(4-Amino-8-benzyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	Tan powder	191-192	Calcd for $C_{24}H_{28}N_4O$: C, 74.20; H, 7.26; N, 14.42. Found: C, 73.93; H, 7.47; N, 14.26.
436	1-(4-Amino-8-benzyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	Yellow crystlas	209-210	Calcd for $C_{24}H_{28}N_4O_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.89; H, 6.87; N, 13.84.

Examples 437-439

Part A

Under a nitrogen atmosphere, cyclohexylmethylamine (40.9 mL, 315 mmol) was added dropwise to a solution of 7-bromo-4-chloro-3-nitroquinoline (30.0 g, 105 mmol) in dichloromethane (524 mL). The reaction was stirred for 18 hours at ambient temperature and then concentrated under reduced pressure. Water (200 mL) was added to the residue, and the mixture was stirred for three hours. Acetonitrile was added; a precipitate formed. The solid was isolated by filtration, dried under a flow of air for two hours, and recrystallized from acetonitrile to provide 24.0 g of (7-bromo-3-nitroquinolin-4-yl)cyclohexylmethylamine as a yellow solid.

Part B

The method described in Part A of Examples 427-429 was used to reduce (7-bromo-3-nitroquinolin-4-yl)cyclohexylmethylamine (24.0 g, 65.9 mmol) to 21.0 g of 7-bromo-N^4-(cyclohexylmethyl)quinoline-3,4-diamine, obtained as a greenish solid.

Part C

A modification of the method described in Part A of Example 9 was used to treat 7-bromo-N^4-(cyclohexylmethyl)quinoline-3,4-diamine (7.3 g, 22 mmol) with ethoxyacetyl chloride (2.75 mL, 24.0 mmol). The reaction was heated overnight at 90 °C and then concentrated under reduced pressure to provide 7-bromo-1-cylcohexylmethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline as a dark brown semi-solid.

Part D

The method described in Part J of Example 365 was used to oxidize and aminate 7-bromo-1-cylcohexylmethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline (7.58 g, 22.0 mmol). 3-Chloroperoxybenzoic acid (9.1 g of 50% pure material, 26.4 mmol) was added in five portions during the oxidation step, and the amination with ammonium hydroxide (55 mL) and *p*-toluenesulfonyl chloride (6.3 g, 33 mmol) proceeded overnight. The crude product was obtained as an oil, which was treated with acetonitrile to form a precipitate. The precipitate was isolated by filtration and washed with a small amount of acetonitrile. A portion of the brown solid was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 95:5 to 85:15) to provide 7-bromo-1-cylcohexylmethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a brown solid, mp 215-216 °C.

Anal. Calcd for $C_{20}H_{25}BrN_4O$: C, 57.56; H, 6.04; N, 13.42. Found: C, 57.57; H, 5.93; N, 13.44.

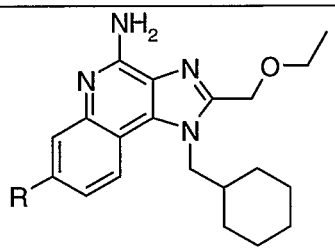
Part E

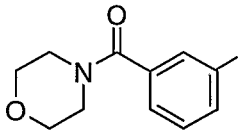
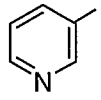
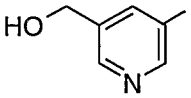
7-Bromo-1-cylcohexylmethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine and the boronic acid indicated in the table below were coupled according to the general methods described in Part J of Example 1 and Part F of Examples 125-135. Palladium (II) acetate was added as a 5 mg/mL

solution in toluene, and the reaction was heated overnight. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 90:10 to 55:45 for Examples 437 and 438 and 95:5 to 85:15 for Example 439) followed by recrystallization from acetonitrile to provide the product shown in the table below.

Example 439 was treated as described in Example 429. The crude product was purified twice by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 90:10 to 70:30) followed by recrystallization from methanol to provide the compound shown in the following table.

Examples 437-439



Example	Boronic Acid	R
437	3-(Morpholine-4-carbonyl)phenylboronic acid	
438	3-Pyridine boronic acid	
439	5-(*tert*-Butyldimethylsilanyloxymethyl) pyridine-3-boronic acid	

Examples 437-439

Example	Name	Form	mp (°C)	Anal.
437	1-[3-(4-Amino-1-cyclohexylmethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl)phenyl]morpholin-4-ylmethanone	Tan needles	186-187	Calcd for $C_{31}H_{37}N_5O_3$: C, 70.56; H, 7.07; N, 13.27. Found: C, 70.16; H, 7.24; N, 13.40.
438	1-Cyclohexylmethyl-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Tan crystals	146-148	Calcd for $C_{25}H_{29}N_5O$: C, 71.95; H, 7.05; N, 16.78. Found: C, 71.60; H, 6.83; N, 16.65.
439	1-Cyclohexylmethyl-2-ethoxymethyl-7-(5-hydroxymethylpyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white crystals	240-241	Calcd for $C_{26}H_{31}N_5O_2$: C, 70.09; H, 7.01; N, 15.72. Found: C, 69.92; H, 6.97; N, 15.61.

Examples 440-463

Part A

(7-Bromo-3-nitroquinolin-4-yl)-(2-methylpropyl)amine (117 g) was dissolved in hot toluene (2 L) and poured into stainless steel Parr vessel. Additional toluene (2 L) and 5% platinum on carbon (12.5 g) were added. The vessel was evacuated, charged with hydrogen (54 psi, 3.7 x 10^5 Pa), and shaken overnight at room temperature. The reaction mixture evacuated, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure to provide 7-bromo-N^4-(2-methylpropyl)quinoline-3,4-diamine, which was used without purification.

Part B

Butyryl chloride (1.1 equivalent) was slowly added to a stirred solution of 7-bromo-N^4-(2-methylpropyl)quinoline-3,4-diamine (52.9 g, 0.18 mol.) in pyridine (700 mL) at room temperature. A pale yellow precipitate formed and then went into solution. The reaction mixture was heated at reflux for eight hours, and then allowed to slowly cool to room temperature over the weekend. The dark gold, turbid reaction mixture was concentrated under reduced pressure. The residue was dissolved in 1 N hydrochloric acid and then adjusted to pH 14 with the addition of 10% aqueous sodium hydroxide. A precipitate formed, was isolated by filtration, washed with water (3x100 mL), and dried overnight on the filter funnel to provide 7-bromo-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid.

Part C

To a stirred solution of 7-bromo-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (51.1 g, 0.148 mol) in dichloromethane (1 L) was slowly added 3-chloroperoxybenzoic acid (1.0 equivalent of 50% pure material) in small portions. The reaction was maintained at room temperature for one hour. Concentrated ammonium hydroxide (600 mL) was added with stirring. After 15 minutes, *p*-toluenesulfonyl chloride (1.1 equivalents.) was added in small portions. The reaction was stirred at room temperature overnight. The reaction was quenched by adding water (1 L) and stirred for an additional hour. A solid was present and was isolated by filtration to provide 7-bromo-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white solid.

Part D

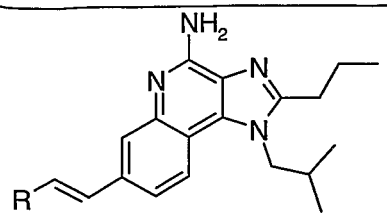
Triethylamine (3.0 equivalents), potassium vinyltrifluoroborate (1.0 equivalent) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.2 equivalent) were added to a solution of 7-bromo-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.0 equivalent) in *n*-propanol (30 ml/g). The reaction mixture was heated at reflux under a nitrogen atmosphere until it was complete (between four and 18 hours) and then poured into water (3 volumes). The pH of the mixture was monitored and

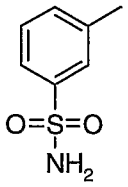
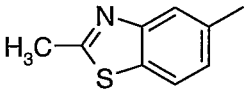
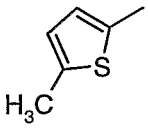
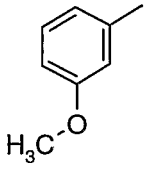
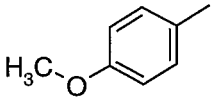
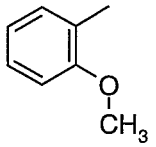
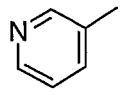
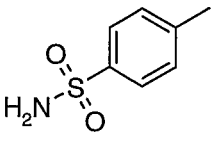
adjusted to pH 12 with the addition of 10% aqueous sodium hydroxide if needed. The mixture was extracted with ethyl acetate, and the combined organic fractions were filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with chloroform:methanol in a gradient from 100:0 to 90:10), followed by recrystallization from acetonitrile to provide 1-(2-methylpropyl)-2-propyl-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white solid.

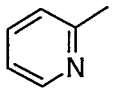
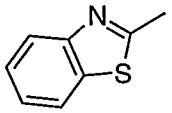
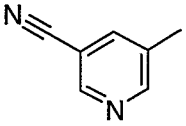
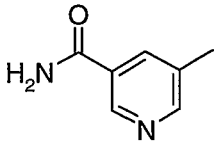
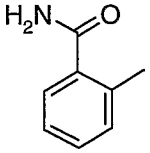
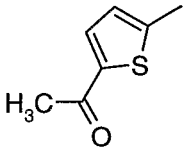
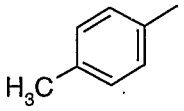
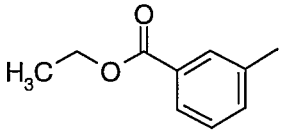
Part E

A thick-walled glass tube, equipped with magnetic stir-bar, was charged with acetonitrile (20 mL/g), palladium (II) acetate (0.1 equivalent), tri-*ortho*-tolylphosphine (0.3 equivalent), triethylamine (3.0 equivalent), 1-(2-methylpropyl)-2-propyl-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.0 equivalent), and the aryl- or heteroaryl-halide (1.5 equivalents) shown in the table below. The tube was purged with nitrogen and sealed. The reaction mixture was heated at 120 °C for between 24 and 48 hours and then allowed to cool to ambient temperature. The solvent was removed under reduced pressure. The solid was then partitioned between dichloromethane and water; the mixture was adjusted to pH 12 with the addition of 10% aqueous sodium hydroxide if needed. The organic layer was separated and was purified by flash column chromatography on silica gel (eluting with chloroform:methanol in a gradient from 100:0 to 90:10) followed by recrystallization from acetonitrile to provide the compound shown in the table below.

Examples 440-455



Example	Aryl- or Heteroaryl halide	R
440	3-Bromobenzenesulfonamide	
441	5-Bromo-2-methylbenzothiazole	
442	2-Iodo-5-methylthiophene	
443	3-Bromoanisole	
444	4-Bromoanisole	
445	2-Bromoanisole	
446	3-Bromopyridine	
447	4-Bromobenzenesulfonamide	

448	2-Bromopyridine	
449	2-Chlorobenzothiazole	
450	5-Bromonicotinonitrile	
451	5-Bromonicotinamide	
452	2-Bromobenzamide	
453	2-Acetyl-5-bromothiophene	
454	4-Bromotoluene	
455	Ethyl 3-bromobenzoate	

The characterization data for Examples 440-446 and Example 452 are shown in the table below.

Examples 440-446, 450, 452

Ex.	Name	Form	Mp (°C)	Anal.
440	(*E*)-3-{2-[4-Amino-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl]vinyl}benzenesulfonamide	White solid	>250	Calcd for $C_{25}H_{29}N_5O_2S$: C, 54.69; H, 5.60; N, 12.77. Found: C, 54.62; H, 5.44; N, 12.65.
441	(*E*)-7-[2-(2-Methylbenzothiazol-5-yl)vinyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white solid	210-212	Calcd for $C_{27}H_{29}N_5S$•1.8 CH_4O: C, 67.22; H, 7.46: N, 13.63. Found: C, 67.07; H, 7.18; N, 13.91.
442	(*E*)-1-(2-Methylpropyl)-7-[2-(5-methylthiophen-2-yl)vinyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Light tan crystals	182-185	Calcd for $C_{24}H_{28}N_4S$: C, 71.25; H, 6.98; N, 13.85. Found: C, 71.01; H, 6.80; N, 13.81.
443	(*E*)-7-[2-(3-Methoxyphenyl)vinyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Pale yellow crystals	181-183	Calcd for $C_{26}H_{30}N_4O$: C, 75.33; H, 7.29; N, 13.51. Found: C, 75.28; H, 7.52; N, 13.77.
444	(*E*)-7-[2-(4-Methoxyphenyl)vinyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white solid	201-202	Calcd for $C_{26}H_{30}N_4O$: C, 75.33; H, 7.29; N, 13.51. Found: C, 75.06; H, 7.44; N, 13.63.
445	(*E*)-7-[2-(2-Methoxyphenyl)vinyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Tan needles	214-216	Calcd for $C_{26}H_{30}N_4O$: C, 75.33; H, 7.29; N, 13.51. Found: C, 75.12; H, 7.68; N, 13.53.

446	(*E*)-1-(2-Methylpropyl)-2-propyl-7-[2-(pyridin-3-yl)vinyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Yellow crystals	190-192	Calcd for $C_{24}H_{27}N_5$•0.5 H2O: C, 73.07; H, 7.15: N, 17.75. Found: C, 73.13; H, 7.33; N, 17.88.
450	(*E*)-3-{2-[4-Amino-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl]vinyl}nicotinonitrile	Yellow solid	246-248	Calcd for $C_{25}H_{26}N_6$: C, 73.14; H, 6.38: N, 20.47. Found: C, 73.15; H, 6.11; N, 20.42.
452	(*E*)-2-{2-[4-Amino-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl]vinyl}benzamide	Tan crystals	Not meas-ured	Calcd for $C_{26}H_{29}N_5O$: C, 73.04; H, 6.84: N, 16.38. Found: C, 72.80; H, 6.79; N, 16.26.

Examples 447-449, 451, 453-455

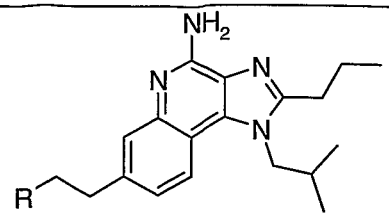
Example	Name	MS (APCI) *m/z* (M + H)$^+$
447	(*E*)-4-{2-[4-Amino-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl]vinyl}benzenesulfonamide	464
448	(*E*)-1-(2-Methylpropyl)-2-propyl-7-[2-(pyridin-2-yl)vinyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine	386
449	(*E*)-7-[2-(Benzothiazol-2-yl)vinyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	442
451	(*E*)-3-{2-[4-Amino-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl]vinyl}nicotinamide	429.3

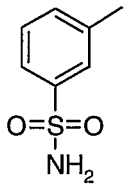
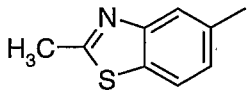
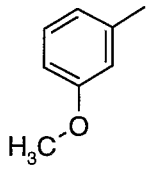
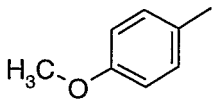
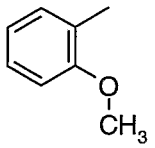
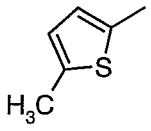
453	(*E*)-7-[2-(2-Acetylthiophen-5-yl)vinyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	433.3
454	(*E*)-1-(2-Methylpropyl)-2-propyl-7-[2-(*p*-tolyl)vinyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine	399.1
455	(*E*)-Ethyl 3-{2-[4-amino-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl]vinyl}benzoate	457.3

Examples 456-461

A Parr hydrogenation vessel was charged with the starting material indicated in the table below, a 1:1 mixture of methanol:ethanol (30 mL/g), and 10% palladium on carbon (50% wt./wt.). The reaction vessel was evacuated, charged with hydrogen (45 psi, 3.1 x 10^5 Pa), and shaken until the reaction was complete (24-48 hours). The reaction mixture was filtered through CELITE filter agent, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 100:0 to 90:10) followed by recrystallization from acetonitrile to provide the product shown in the table below.

Examples 456-461



Example	Starting Material	R
456	Example 440	
457	Example 441	
458	Example 443	
459	Example 444	
460	Example 445	
461	Example 442	

The characterization data for Examples 456-461 are shown in the table below.

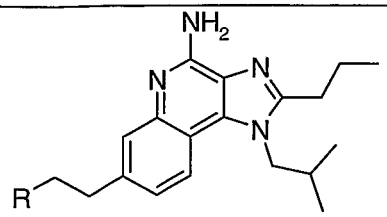
Examples 456-461

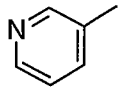
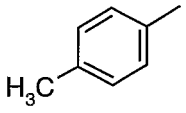
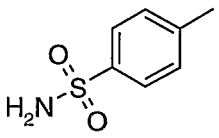
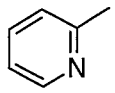
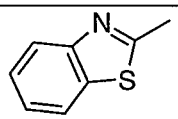
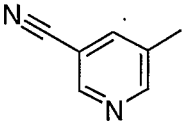
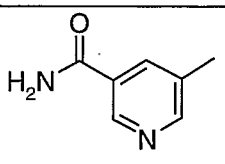
Example	Name	Form	mp (°C)	Anal.
456	3-{2-[4-Amino-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-7-yl]ethyl}benzenesulfonamide	Off-white solid	250-251	Calcd for $C_{25}H_{31}N_5O_2S$: C, 64.49; H, 6.71; N, 15.04. Found: C, 64.28; H, 6.76; N, 14.88.
457	7-[2-(2-Methylbenzothiazol-5-yl)ethyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	>250	Calcd for $C_{27}H_{31}N_5S$•HCl: C, 65.63; H, 6.53: N, 14.17. Found: C, 65.68; H, 6.73; N, 13.96.
458	7-[2-(3-Methoxyphenyl)ethyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White crystals	155-157	Calcd for $C_{26}H_{32}N_4O$: C, 74.97; H, 7.74; N, 13.45. Found: C, 74.57; H, 7.65; N, 13.52.
459	7-[2-(4-Methoxyphenyl)ethyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	>250	Calcd for $C_{26}H_{32}N_4O$•HCl: C, 68.93; H, 7.34: N, 12.37. Found: C, 68.67; H, 7.82; N, 12.33.
460	7-[2-(2-Methoxyphenyl)ethyl]-1-(2-methylpropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White solid	>250	Calcd for $C_{26}H_{32}N_4O$•HCl: C, 68.93; H, 7.34: N, 12.37. Found: C, 68.76; H, 7.69; N, 12.29.
461	1-(2-Methylpropyl)-7-[2-(5-methylthiophen-2-yl)ethyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white solid	150-152	Calcd for $C_{24}H_{30}N_4S$: C, 70.90; H, 7.44; N, 13.78. Found: C, 71.28; H, 7.70; N, 13.80.

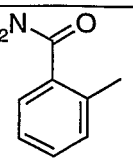
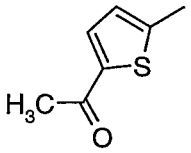
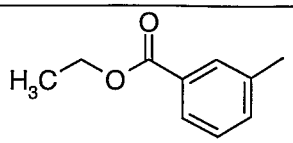
Examples 462-471

The procedure described in Examples 456-461 can also be used to hydrogenate the following compounds to provide the products shown in the table below.

Examples 462-471

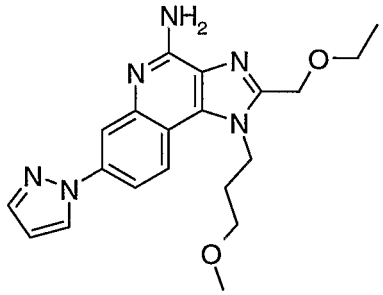


Example	Starting Material	R
462	Example 446	
463	Example 454	
464	Example 447	
465	Example 448	
466	Example 449	
467	Example 450	
468	Example 451	

469	Example 452	
470	Example 453	
471	Example 455	

Example 472

2-Ethoxymethyl-1-(3-methoxypropyl)-7-(pyrazol-1-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

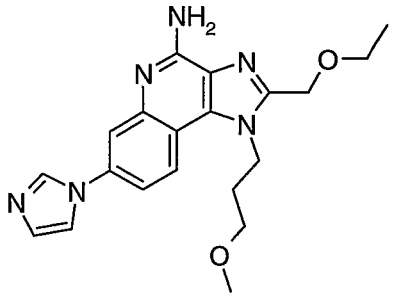


A 4 dram vial containing a stir bar was charged sequentially with copper(I) iodide (0.038 g), potassium phosphate (0.890 g), pyrazole (0.164 g), 7-bromo-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.786 g), (±)-*trans*-1,2-diaminocyclohexane (0.030 mL), and anhydrous 1,4-dioxane (2mL). The vial was flushed with nitrogen, capped, and placed in an oil bath at 110°C. After 15.5 hours, the reaction was cooled to room temperature and purified by flash column chromatography using a gradient of CMA/chloroform as the eluent. Subsequent recrystallization from acetonitrile yielded 0.190 g of 2-ethoxymethyl-1-(3-methoxypropyl)-7-(pyrazol-1-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 159.0-160.0 °C.

Anal Calcd. for $C_{20}H_{24}N_6O_2$: %C, 63.14; %H, 6.36; %N, 22.09. Found: %C, 62.91; %H, 6.32; %N, 22.06.

Example 473

2-Ethoxymethyl-7-(imidazol-1-yl)-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

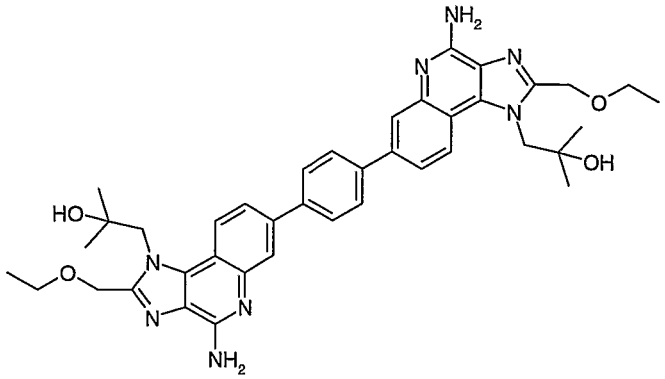


The general method described in Example 452 was followed with imidazole replacing pyrazole as a reactant. After cooling to room temperature, the reaction mixture was poured into water and diluted with dichloromethane. The mixture was stirred for 10 minutes, followed by separation of the layers. The aqueous fraction was extracted with dichloromethane and the combined organic fractions were concentrated. The residue was initially purified by HPFC eluting with a linear gradient of 1-30% CMA in chloroform. A final recrystallization from acetonitrile provided 0.070 g of 2-ethoxymethyl-7-(imidazol-1-yl)-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white solid, mp 167.5-169.0 °C.

Anal Calcd. for $C_{20}H_{24}N_6O_2$: %C, 63.14; %H, 6.36; %N, 22.09. Found: %C, 63.11; %H, 6.30; %N, 22.16.

Example 474

1-(4-Amino-7-{4-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol

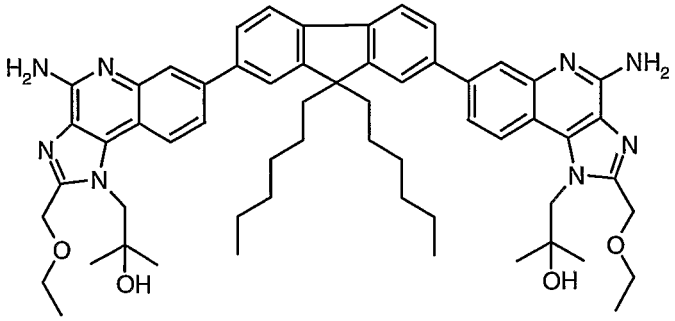


A mixture of 1-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (2.18 g, 5.54 mmol), 1,4-phenylenebisboronic acid (0.44 g, 2.65 mmol), triphenylphosphine (42 mg, 0.16 mmol), *n*-propanol (36 mL), 2 M aqueous sodium carbonate (3.2 mL, 6.4 mmol), and water was degassed three times and placed under a nitrogen atmosphere. Palladium (II) acetate (12 mg, 0.050 mmol) in 250 µL of warm toluene was added, and reaction was degassed twice and placed under a nitrogen atmosphere. The reaction was heated at 100 °C for one hour and then allowed to cool to ambient temperature. A precipitate formed and was isolated by filtration, recrystallized from ethanol (300 mL), isolated by filtration, washed with ethanol, and dried in a vacuum oven at 60 °C to provide 286 mg of 1-(4-amino-7-{4-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as off-white needles, mp 325-328 °C.

Anal. Calcd for $C_{40}H_{46}N_8O_4 \cdot 1.4\ H_2O$: C, 65.99; H, 6.76; N, 15.39. Found: C, 65.86; H, 6.80; N, 15.39.

Example 475

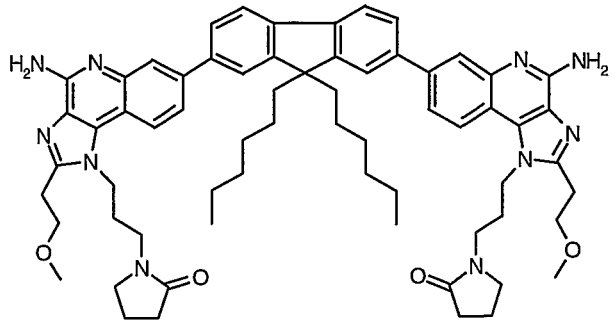
1-(4-Amino-7-{7-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-9,9-dihexyl-9*H*-fluoren-2-yl}-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol



1-(4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (2.18 g, 5.54 mmol) and 9,9-dihexylfluorene-2,7-diboronic acid (1.12 g, 2.65 mmol) were coupled according to the method described in Example 474. At the completion of the reaction, the *n*-propanol was removed under reduced pressure, and the residue was dissolved in dichloromethane (150 mL). The resulting solution was washed sequentially with 2 M aqueous sodium carbonate (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 75:25) followed by recrystallization from dichloromethane (15 mL) and heptane (30 mL). The solid was isolated by filtration, washed with heptane, and dried overnight in a vacuum oven at 60 °C to provide 0.68 g of 1-(4-amino-7-{7-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-9,9-dihexyl-9*H*-fluoren-2-yl}-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as off-white needles, mp 261-265 °C. Anal. Calcd for $C_{59}H_{74}N_8O_4 \cdot 1.1\ H_2O$: C, 72.35; H, 7.85; N, 11.44. Found: C, 72.24; H, 7.99; N, 11.47.

Example 476

1-[4-Amino-7-(7-{4-amino-2-(2-methoxyethyl)-1-[3-(pyrrolidin-2-one)propyl]-1*H*-imidazo[4,5-*c*]quinolin-7-yl}-9,9-dihexyl-9*H*-fluoren-2-yl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one



1-{3-[4-Amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one (0.91 g, 2.0 mmol) and 9,9-dihexylfluorene-2,7-diboronic acid (0.41 g, 0.97 mmol) were coupled according to the method described in Example 474; the work-up procedure described in Example 475 was followed. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 90:10 to 65:35) followed by recrystallization from isopropanol (40 mL). The solid was isolated by filtration, washed with isopropanol, and dried over three days in a vacuum oven at 60 °C to provide 0.45 g of 1-[4-amino-7-(7-{4-amino-2-(2-methoxyethyl)-1-[3-(pyrrolidin-2-one)propyl]-1*H*-imidazo[4,5-*c*]quinolin-7-yl}-9,9-dihexyl-9*H*-fluoren-2-yl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one as off-white needles, mp 251-254 °C.

Anal. calcd for $C_{65}H_{80}N_{10}O_4 \cdot 0.8\ H_2O$: C, 72.27; H, 7.62; N, 12.97. Found: C, 72.07; H, 7.84; N, 12.99.

Examples 477-480

Part A

Ammonium hydroxide (1 L) was added to a solution of methyl tetrahydropyranyl acetate (20 mL, 150 mmol) in methanol (500 mL), and the reaction was stirred overnight at ambient temperature. Additional ammonium hydroxide (500 mL) was added, and the reaction was stirred for four additional days. The methanol was removed under reduced pressure. Solid sodium

chloride was added to the aqueous layer, which was extracted with chloroform (3 x 150 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 11.4 g of tetrahydropyran-4-carboxamide as a white solid.

Part B

A solution of tetrahydropyran-4-carboxamide (11.4 g, 88.3 mmol) in THF (441 mL) was cooled to 0 °C. Lithium aluminum hydride (10.0 g, 265 mmol) was added in six portions over a period of ten minutes. The reaction flask was purged with nitrogen between the additions. When the reaction mixture was no longer bubbling, it was heated at reflux for six hours. The reaction was then cooled to 0 °C, and ethyl acetate was added dropwise until bubbling ceased. Methanol was then added dropwise until bubbling ceased. Water (10 mL), 15% aqueous sodium hydroxide (10 mL), and water (30 mL) were sequentially added. The organic fraction was decanted off, and the remaining gray solid was washed with chloroform. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide *C*-(tetrahydropyran-4-yl)methylamine.

Part C

The method described in Part E of Examples 431-436 was used to treat 7-bromo-4-chloro-3-nitroquinoline (12.43 g, 43.45 mmol) with *C*-(tetrahydropyran-4-yl)methylamine (10 g, 87 mmol) to provide 15.0 g of (7-bromo-3-nitroquinolin-4-yl)(tetrahydropyran-4-ylmethyl)amine as a bright yellow solid.

Part D

The method described in Part A of Examples 427-429 was used to reduce (7-bromo-3-nitroquinolin-4-yl)(tetrahydropyran-4-ylmethyl)amine (15.0 g, 44.0 mmol) to 7-bromo-N^4-(tetrahydropyran-4-ylmethyl)quinoline-3,4-diamine, obtained as a greenish solid.

Part E

The material from Part D was treated with ethoxyacetyl chloride (5.5 mL, 48 mmol) according to the method described in Part A of Example 9. The reaction was heated overnight, and after the work-up procedure, the crude

product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) to provide 9.3 g of 7-bromo-2-ethoxymethyl-1-(tetrahydropyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an oil.

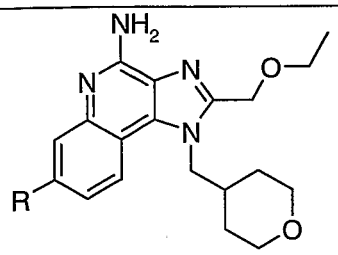
Part F

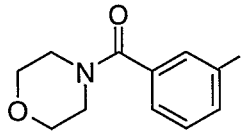
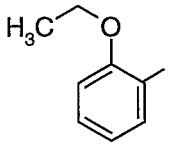
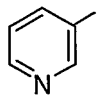
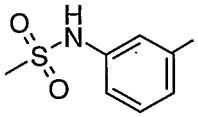
The method described in Part J of Example 365 was used to oxidize and aminate 7-bromo-2-ethoxymethyl-1-(tetrahydropyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (9.3 g, 23.0 mmol). 3-Chloroperoxybenzoic acid (7.9 g of 50% pure material, 23 mmol) was added in five portions during the oxidation step, which was stirred overnight. Additional 3-chloroperoxybenzoic acid (200 mg) was added, and the reaction was stirred for 20 mintues before ammonium hydroxide (60 mL) and *p*-toluenesulfonyl chloride (6.58 g, 34.5 mmol) were added. The crude product was obtained as an oil, which was treated with acetonitrile to form a precipitate. The precipitate was isolated by filtration and purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) to provide 6.0 g of 7-bromo-2-ethoxymethyl-1-(tetrahydropyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 186-188 °C.

Part G

7-Bromo-2-ethoxymethyl-1-(tetrahydropyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine and the boronic acid indicated in the table below were coupled according to the general methods described in Part J of Example 1 and Part F of Examples 125-135. Palladium (II) acetate was added as a 5 mg/mL solution in toluene, and the reaction was heated overnight. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30). The resulting oil was stirred with a small amount of acetonitrile to provide a solid, which was isolated by filtration. For Examples 477 and 478, the solid was recrystallized twice from acetonitrile to provide the product shown in the table below. For Examples 479 and 480, the solid was allowed to dry in the filter funnel to provide the product shown in the table below.

Examples 477-480



Example	Boronic Acid	R
477	3-(Morpholine-4-carbonyl)phenylboronic acid	
478	2-Ethoxyphenylboronic acid	
479	3-Pyridine boronic acid	
480	3-(Methylsulfonylamino)phenylboronic acid	

The characterization data for Examples 477-480 are provide in the table below.

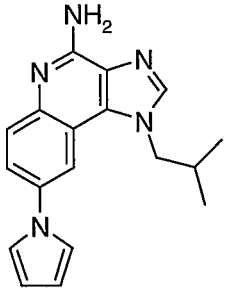
Examples 477-480

Example	Name	Form	mp (°C)	Anal.
477	{3-[4-Amino-2-ethoxymethyl-1-(tetrahydropyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}morpholin-4-ylmethanone	White crystals	125-128	Calcd for $C_{30}H_{35}N_5O_4 \cdot 0.2 H_2O$: C, 66.67; H, 6.75; N, 12.96. Found: C, 66.34; H, 6.75; N, 12.99.

478	2-Ethoxymethyl-7-(2-ethoxyphenyl)-1--(tetrahydropyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Yellow crystals	192-193	Calcd for $C_{27}H_{32}N_4O_3 \cdot 0.06 H_2O$: C, 70.25; H, 7.01; N, 12.14. Found: C, 69.85; H, 7.37; N, 12.32.
479	2-Ethoxymethyl-7-(pyridin-3-yl)-1-(tetrahydropyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	White powder	116-121	Calcd for $C_{24}H_{27}N_5O_2 \cdot 0.09 H_2O$: C, 68.78; H, 6.54; N, 16.71. Found: C, 68.89; H, 6.94; N, 16.73.
480	{3-[4-Amino-2-ethoxymethyl-1-(tetrahydropyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]phenyl}methanesulfonamide	White powder	254-255	Calcd for $C_{26}H_{31}N_5O_4S$: C, 61.28; H, 6.13; N, 13.74. Found: C, 60.96; H, 6.46; N, 13.99.

Example 481

1-(2-Methylpropyl)-8-(1-pyrrolyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (28.3 g, 0.118 mol) in concentrated sulfuric acid (150 mL) was cooled to 5 °C. A solution of 70% nitric acid (8.4 mL, 0.130 mol) in sulfuric acid (30 mL) was added in portions over a period of one hour. The reaction temperature was

maintained below 10 °C. The solution was allowed to warm to ambient temperature, stirred for two hours, and then poured into 500 g of ice. The resulting solution was made basic with the addition of ammonium hydroxide while keeping the solution cold. A precipitate formed, was isolated by filtration, washed with water, and dried to provide 1-(2-methylpropyl)-8-nitro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow solid.

Part B

The material from Part A was added slowly with stirring to a solution of 98% tin (II) chloride (114 g, 0.589 mmol) in concentrated hydrochloric acid (500 mL), and the reaction was heated at 100 °C for 15 minutes, allowed to cool to ambient temperature, and cooled to 0 °C. A precipitate formed and was isolated by filtration, washed with a small amount of ethanol, and suspended in water. The suspension was adjusted to pH 13-14, and the resulting precipitate was isolated by filtration, washed with water, and mixed with water. The resulting suspension was made acidic with the addition of 6 N aqueous hydrochloric acid and then filtered. The filtrate was adjusted to pH 13-14 to form a precipitate, which was isolated by filtration, washed with water, and dried to provide 21.8 g of 8-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a solid.

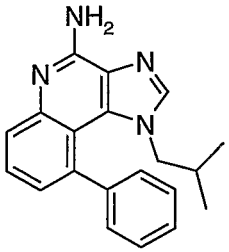
Part C

2,5-Dimethoxytetrahydrofuran (1.6 mL of 95%, 12 mmol) was added to a suspension of 8-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3.0 g, 12 mmol) in acetic acid (60 mL), and the reaction was heated at reflux for one hour. The resulting dark brown solution was concentrated under reduced pressure, and the residue was mixed with water. The resulting mixture was made basic with the addition of ammonium hydroxide and stirred for 30 minutes. The resulting precipitate was isolated by filtration, washed with water, dried, and recrystallized from ethanol (100 mL). The crystals were collected in three crops. The first crop was dried for a day in a vacuum oven at 100 °C to provide 2.1 g of 1-(2-methylpropyl)-8-(1-pyrrolyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a solid, mp 227.5-231.5 °C.

Anal. Calcd for $C_{18}H_{19}N_5$: C, 70.8; H, 6.3; N, 22.9. Found: C, 70.6; H, 6.3; N, 23.1.

Example 482

1-(2-Methylpropyl)-9-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

5-[(3-Bromophenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (32.6 g, 0.100 mol) was heated at 250 °C in DOWTHERM A heat transfer fluid for one hour, and then the reaction was allowed to cool to ambient temperature. A precipitate formed upon cooling and was isolated by filtration and washed with diethyl ether to provide 7-bromoquinolin-4-ol and 5-bromoquinolin-4-ol in a 2:1 ratio.

Part C

The method described in Part D of Example 10 was used to treat the material from Part A with nitric acid (10.3 mL of 11.74 M, 0.121 mmol) to provide 18.0 g of a 2:1 mixture of 7-bromo-3-nitroquinolin-4-ol and 5-bromo-3-nitroquinolin-4-ol.

Part D

The method described in Part D of Example 1 was used to treat 7-bromo-3-nitroquinolin-4-ol and 5-bromo-3-nitroquinolin-4-ol (10.0 g, 37.0 mmol) with phosphorous oxychloride (32.0 mL of 1.16 M) to provide a 2:1 mixture of 7-bromo-4-chloro-3-nitroquinoline and 5-bromo-4-chloro-3-nitroquinoline.

Part E

Under a nitrogen atmosphere, isobutylamine (11.0 mL, 0.111 mol) was added to the material from Part D and triethylamine (11.0 mL, 0.111 mol) in dichloromethane (15 mL). The reaction was stirred for 30 minutes at ambient temperature, and the volatiles were removed under reduced pressure to provide a 2:1 mixture of (7-bromo-3-nitroquinolin-4-yl)isobutylamine and (5-bromo-3-nitroquinolin-4-yl)isobutylamine containing some triethylamine.

Part F

A solution of sodium hydrosulfite (3.2 g, 185 mmol) in water (8 mL) was added to a solution of the material from Part E in 1:1 ethanol:acetonitrile (300 mL), and the reaction was stirred at ambient temperature for one hour. The solvents were removed under reduced pressure, and the resulting mixture was diluted with water. The aqueous mixture was extracted with chloroform (3 x). The combined extracts were purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20); the first compound to elute was 5-bromo-N^4-(2-methylpropyl)quinoline-3,4-diamine. Following the purification 2.2 g of this compound were isolated.

Part G

A mixture of 5-bromo-N^4-(2-methylpropyl)quinoline-3,4-diamine (1.0 g, 3.4 mmol), triethyl orthoformate (0.9 mL, 5 mmol), and pyridine hydrochloride (117 mg, 1.0 mmol) in acetonitrile (17 mL) was heated at reflux overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) to provide 9-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline as a dark oil.

Part H

9-Bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (0.34 mmol) and benzene boronic acid (62 mg, 0.51 mmol) were coupled according to Part J of Example 1. The work-up procedure described in Parts 125-135 was followed. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 85:15) to provide 1-(2-methylpropyl)-9-phenyl-1*H*-imidazo[4,5-*c*]quinoline.

Part I

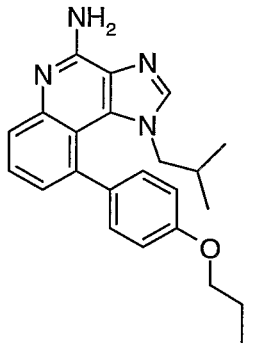
The method described in Part J of Example 365 was used to oxidize and aminate 1-(2-methylpropyl)-9-phenyl-1*H*-imidazo[4,5-*c*]quinoline (0.34 mmol). The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 85:15) to provide 40 mg of 1-(2-methylpropyl)-9-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a pale yellow powder, mp 263-265 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.55-7.39 (m, 6H), 7.12 (d, J = 7.2 Hz, 1H), 6.65 (broad s, 2H), 2.57 (d, J = 7.6 Hz, 2H), 1.48 (m, 1H), 0.22 (d, J = 6.7 Hz, 6H);

MS (ESI) *m/z* 317.1770 (calcd for $C_{20}H_{20}N_4$ 317.1766, $M+H^+$).

Example 483

1-(2-Methylpropyl)-9-(4-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

9-Bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (1.0 g, 3.4 mmol) and 4-propoxyphenylboronic acid (1.0 g, 5.5 mmol) were coupled according to Part J of Example 1. The palladium (II) acetate (2.5 mg, 0.011 mmol) was added as a 5 mg/mL solution in toluene. The work-up procedure described in Parts 125-135 was followed. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) to provide 1.1 g of 1-(2-methylpropyl)-9-(4-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinoline as a dark brown oil.

Part I

The method described in Part J of Example 365 was used to oxidize and aminate 1-(2-methylpropyl)-9-(4-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinoline (1.1 g, 3.1 mmol). The amination reaction was stirred for 36 hours. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) to provide an oil, which was stirred with acetonitrile to provide a solid. The solid was isolated by filtration and recrystallized from acetonitrile to provide 165 mg of 1-(2-methylpropyl)-9-(4-propoxyphenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as light tan needles, mp 181-182 °C.

Anal. Calcd for $C_{23}H_{26}N_4O \cdot 0.2\ H_2O$: C, 73.07; H, 7.04; N, 14.82. Found: C, 72.70; H, 6.90; N, 14.87.

Examples 484-486

Part A

Diethyl malonate (101 mL, 0.989 mol) and 2-bromoaniline (50.g, 0.291 mol) were combined and heated at 180 °C for six hours. A Dean-Stark trap was used to collect the volatiles. The reaction was allowed to cool to ambient temperature overnight; a precipitate formed. The precipitate was isolated by filtration and combined with methanol (160 mL), water (800 mL), and solid sodium carbonate (105 g). The mixture was heated at reflux for two hours, allowed to cool to ambient temperature, and then cooled to 0 °C. The mixture was adjusted to pH 2 with the addition of 3 N hydrochloric acid; a white precipitate formed. The precipitate was isolated by filtration, washed with water, and dried overnight on the filter funnel to provide 43 g of *N*-(2-bromophenyl)malonamic acid as a white solid.

Part B

N-(2-Bromophenyl)malonamic acid (43 g, 170 mmol), polyphosphoric acid (334 mL of 0.5 M), and hydrochloric acid (444 mL of 1 N) were combined and heated at 140 °C for three hours. The solution was allowed to cool to ambient temperature, and additional hydrochloric acid (603 mL of 1 N) was added. The reaction was stirred for four hours and then adjusted to pH 4 with the addition of 20% aqueous sodium hydroxide. A precipitate formed and was isolated by filtration, washed with water, and dried to provide 37.4 g of 8-bromoquinoline-2,4-diol as a solid.

Part C

A modification of the method described in Part D of Example 10 was used to treat 8-bromoquinoline-2,4-diol (10.0g, 41.6 mmol) with nitric acid (3.6 mL of 11.74 M, 54 mmol). The nitric acid was added at ambient temperature, and then the reaction was heated at 100 °C for one hour, at which time an exotherm occurred. The reaction was allowed to cool to ambient temperature; a precipitate formed and was isolated by filtration and washed with a small

volume of water to provide 7.58 g of 8-bromo-3-nitroquinoline-2,4-diol as a yellow solid.

Part D

A mixture of phenylphosphonic dichloride (14.1 mL of 90% pure material, 99.3 mmol) and 8-bromo-3-nitroquinoline-2,4-diol (7.08 g, 24.8 mmol) was heated at 140 °C for three hours and then allowed to cool to ambient temperature. Ice water was added, and the mixture was stirred for 20 minutes to form a precipitate. The precipitate was isolated by filtration to provide 8-bromo-2,4-dichloro-3-nitroquinoline as a solid.

Part E

1-Amino-2-methylpropan-2-ol (2.08 g, 24.8 mmol) and triethylamine (10.4 mL, 74.4 mmol) were added to a solution of the material from Part D in dichloromethane (73 mL), and the reaction was stirred for 30 minutes. The solvent and some of the amines were removed under reduced pressure, and the residue was diluted with water. The aqueous layer was separated and extracted with chloroform, and the combined organic fractions were purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) to provide 1-(8-bromo-2-chloro-3-nitroquinolin-4-ylamino)-2-methylpropan-2-ol as a yellow solid.

Part F

The method described in Part F of Example 482 was used to reduce the material from Part E with sodium hydrosulfite (25.4 g, 124 mmol) to provide 5.15 g of 1-(3-amino-8-bromo-2-chloroquinolin-4-ylamino)-2-methylpropan-2-ol as a brown oil.

Part G

A solution of 1-(3-amino-8-bromo-2-chloroquinolin-4-ylamino)-2-methylpropan-2-ol (4.65 g, 14.4 mmol) and ethoxyacetyl chloride (1.9 mL, 15.8 mmol) in dichloromethane (72 mL) was stirred for one hour at ambient temperature. The solvent was removed under reduced pressure, and ethanol (43 mL), water (29 mL), and potassium carbonate (3.98 g, 28.8 mmol) were added. The reaction was stirred at 40 °C for 36 hours. The solvent was removed under reduce pressure, and the residue was diluted with water. The aqueous solution

was extracted with chloroform, and the combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 4.4 g of 1-(6-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as an orange solid.

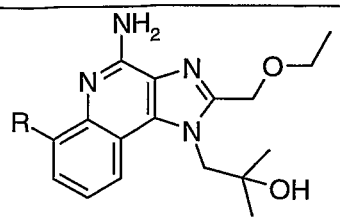
Part H

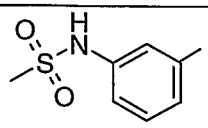
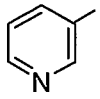
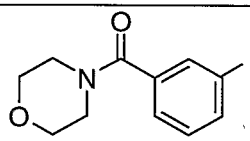
Ammonia (50 mL of a 7 N solution in methanol) and 1-(6-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (4.4 g, 11 mmol) were heated at 120 °C for 72 hours in a high-pressure vessel. The solvent was removed under reduced pressure to provide 3.5 g of a tan powder. The powder was dissolved in chloroform, washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 1-(4-amino-6-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol as a tan solid.

Part I

1-(4-Amino-6-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (842 mg, 2.14 mmol) and the boronic acid indicated in the table below (2.56 mmol) were coupled according to the procedure described in Part J of Example 1. Palladium (II) acetate was added as a 5 mg/mL solution in toluene. The reaction was heated for 15-17 hours at which time additional palladium (II) acetate (1.5 mg) and optionally additional boronic acid were added, and the reaction was heated for an additional 16 hours. The work-up procedure described in Examples 125-135 was followed. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 70:30) followed by recrystallization from the solvent indicated in the table below. For Example 484, a second purification by HPFC, and the resulting oil was triturated with acetonitrile to provide a solid. The structures of the products are shown in the table below.

Examples 484-486



Example	Boronic Acid	Recrystallization Solvent	R
484	3-(Methylsulfonylamino)phenylboronic acid	Acetonitrile	
485	3-Pyridine boronic acid	Methanol	
486	3-(Morpholine-4-carbonyl)phenylboronic acid	Acetonitrile	

The characterization data for Examples 484-486 are shown in the table below.

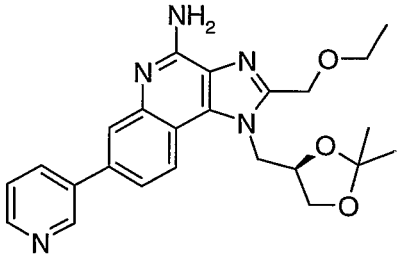
Examples 484-486

Example	Name	Form	mp (°C)	Anal.
484	{3-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-6-yl]phenyl}methanesulfonamide	White powder	234-235	Calcd for $C_{24}H_{29}N_5O_4S$: C, 59.61; H, 6.04; N, 14.48. Found: C, 59.56; H, 6.30; N, 14.55.

485	1-[4-Amino-2-ethoxymethyl-6-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	Tan crystals	199-201	Calcd for $C_{22}H_{25}N_5O_2$: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.38; H, 6.49; N, 17.92.
486	{3-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-6-yl]phenyl}morpholin-4-ylmethanone	Tan crystals	164-166	Calcd for $C_{28}H_{33}N_5O_4$: C, 66.78; H, 6.60; N, 13.91. Found: C, 66.61; H, 6.58; N, 13.91.

Example 487

(*R*)-1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

7-Bromo-4-chloro-3-nitroquinoline (22.00 g, 76.52 mmol) was treated with (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanamine (11.61 g, 114.8 mmol) according to the method described in Part A of Examples 152-156. The crude product was triturated with water (200 mL), isolated by filtration, washed with water, dried, and suspended in diethyl ether (100 mL). The suspension was sonicated, and the resulting solid was isolated by filtration, and dried for four hours in a vacuum oven at 40 °C to provide 25.84 g of (*R*)-(7-bromo-3-nitroquinolin-4-yl)-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)amine as a yellow solid, mp 136-137 °C.

Anal. Calcd for $C_{15}H_{16}BrN_3O_4$: C, 47.14; H, 4.22; N, 10.99. Found: C, 46.78; H, 3.93; N, 10.90.

Part B

The methods described in Parts B, C, and D of Examples 152-156 were used to treat (*R*)-(7-bromo-3-nitroquinolin-4-yl)-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)amine (25.8 g, 67.5 mmol). Triethylamine (11.3 mL, 81.2 mmol) was added in Part C, and after the reaction was stirred for four hours, it was concentrated under reduced pressure and used in Part D. Following chromatographic purification in Part D (eluting with 95:5 chloroform:CMA), the resulting white solid was recrystallized from acetonitrile to provide 17.37 g of (*R*)-7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline as a white, crystalline solid, mp 90-91 °C.

Anal. Calcd for $C_{19}H_{22}BrN_3O_3$: C, 54.30; H, 5.28; N, 10.00. Found: C, 54.37; H, 5.06; N, 9.94.

Part C

(*R*)-7-Bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline (17.37 g, 41.22 mmol) was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized. The product from amination was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 100:0 to 90:10) followed by recrystallization from acetonitrile to provide 7.48 g of (*R*)-7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 176-177 °C.

Anal. Calcd for $C_{19}H_{23}BrN_4O_3 \bullet 0.25\ H_2O$: C, 51.89; H, 5.39; N, 12.74. Found: C, 52.10; H, 5.31; N, 12.88.

Part D

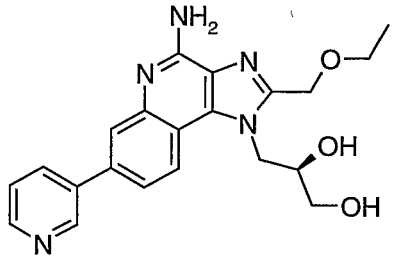
(*R*)-7-Bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3.0 g, 6.9 mmol) and pyridine-3-boronic acid (1.02 g, 8.27 mmol) were coupled according to the method described in Examples 118-121. The work-up procedure described in Part F of Examples 125-135 was followed. The crude product was purified by

HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) followed by recrystallization from acetonitrile to provide 1.96 g of (*R*)-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white, crystalline solid, mp 155-156 °C.

Anal. Calcd for $C_{24}H_{27}N_5O_3$: C, 66.50; H, 6.28; N, 16.15. Found: C, 66.37; H, 6.22; N, 16.37.

Example 488

(*R*)-3-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propane-1,2-diol

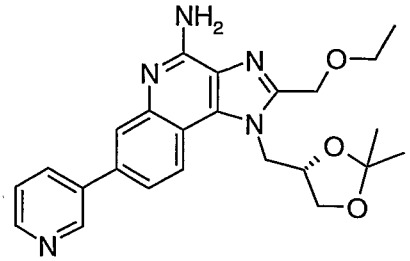


(*R*)-1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.0 g, 2.3 mmol) was treated according to the method Example 162. The product was recrystallized from methanol to provide 0.60 g of (*R*)-3-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propane-1,2-diol as a white, crystalline solid, mp 202-204 °C.

Anal. Calcd for $C_{21}H_{23}N_5O_3 \bullet 0.5\ H_2O$: C, 62.67; H, 6.01; N, 17.40. Found: C, 62.58; H, 5.99; N, 17.29.

Example 489

(*S*)-1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

7-Bromo-4-chloro-3-nitroquinoline (11.00 g, 38.26 mmol) was reacted with (*S*)-2,2-dimethyl-[1,3]dioxolane-4-methanamine (5.81 g, 57.4 mmol) according to the method described in Part A of Examples 125-135. When the reaction was complete, it was concentrated under reduced pressure, and the residue was stirred with water (100 mL). The resulting solid was isolated by filtration, mixed twice with ethanol and concentrated under reduced pressure. The solid was then triturated with diethyl ether, isolated by filtration, and dissolved in dichloromethane. An insoluble impurity was removed by filtration, and the filtrate was concentrated under reduced pressure to provide 14.05 g of (*S*)-(7-bromo-3-nitroquinolin-4-yl)-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)amine as a yellow solid.

Part B

The methods described in Parts B, C, and D of Examples 152-156 were used to treat (*S*)-(7-bromo-3-nitroquinolin-4-yl)-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)amine (10.7 g, 30.4 mmol). Triethylamine (4.67 mL, 33.5 mmol) was added in Part C, and after the reaction was stirred for 1.5 hours, additional reagents were added. The reaction was stirred for an additional four hours before it was concentrated under reduced pressure and used in Part D. Following purification in Part D by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 78:22), the resulting white solid was mixed with diethyl ether to form a solid. The solid was isolated by filtration to provide 8.88 g of (*S*)-7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline as a white solid, mp 89-90 °C.

Anal. Calcd for $C_{19}H_{22}BrN_3O_3$: C, 54.30; H, 5.28; N, 10.00. Found: C, 54.31; H, 5.25; N, 10.00.

Part C

(*S*)-7-Bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline (8.74 g, 20.8 mmol) was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized. The product from amination was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) followed by recrystallization from acetonitrile to provide 4.28 g of (*S*)-7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 184-185 °C.

Anal. Calcd for $C_{19}H_{23}BrN_4O_3$: C, 52.42; H, 5.33; N, 12.87. Found: C, 52.41; H, 5.13; N, 12.91.

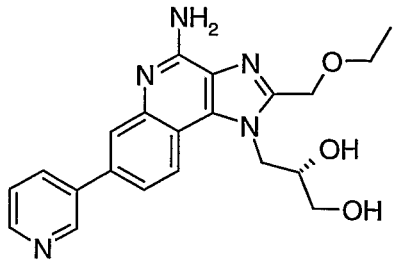
Part D

(*S*)-7-Bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.65 g, 6.09 mmol) and pyridine-3-boronic acid 1,3-propanediol cyclic ester (1.19 g, 7.30 mmol) were coupled according to the method described in Examples 118-121. The work-up procedure described in Part F of Examples 125-135 was followed. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) followed by recrystallization from acetonitriled to provide 1.43 g of (*S*)-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 157-158 °C.

Anal. Calcd for $C_{24}H_{27}N_5O_3 \bullet 0.3H_2O$: C, 65.68; H, 6.34; N, 15.96. Found: C, 65.76; H, 6.24; N, 16.05.

Example 490

(*S*)-3-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propane-1,2-diol

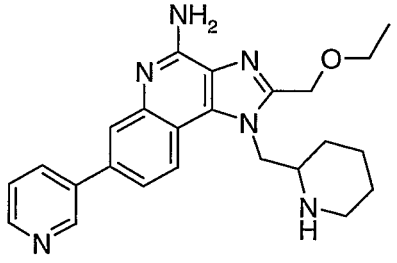


(*S*)-1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.72 g, 1.66 mmol) was treated according to the method Example 162. The product was recrystallized from methanol to provide 0.38 g of (*S*)-3-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propane-1,2-diol as a white, crystalline solid, mp 203-204 °C.

Anal. Calcd for $C_{21}H_{23}N_5O_3 \bullet 0.25\ H_20$: C, 63.38; H, 5.95; N, 17.60. Found: C, 63.41; H, 6.02; N, 17.61.

Example 491

2-Ethoxymethyl-1-(piperidin-2-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride



Part A

7-Bromo-4-chloro-3-nitroquinoline (12.08 g, 42.0 mmol) was treated according to the methods described in Parts A through D of Examples 152-156 using 1-(*tert*-butoxycarbonyl)-2-(aminomethyl)piperidine (10.0 g, 46.7 mmol) in Part A. The product from Part A was triturated with diethyl ether and isolated by filtration. Triethylamine (1.1 equivalents) was added to the reaction in Part C. At the completion of the reaction in Part C, the solvent was removed under

reduced pressure, and the residue was used in Part D. Following chromatographic purification in Part D (eluting with chloroform:CMA in a gradient from 100:0 to 98:2), *tert*-butyl 2-[(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate was obtained as a light yellow solid.

Part B

tert-Butyl 2-[(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate (8.68 g, 17.24 mmol) was oxidized and then aminated according to the methods described in Parts H and I of Example 1. The oxidation product was not recrystallized. The product from amination was purified by flash column chromatography on silica gel (eluting with chloroform:CMA in a gradient from 100:0 to 90:10) to provide *tert*-butyl 2-[(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate as a white solid, mp 190-192 °C.

Anal. Calcd for $C_{24}H_{32}BrN_5O_3$: C, 55.60; H, 6.22; N, 13.51. Found: C, 55.52; H, 6.20; N, 13.31.

Part C

tert-Butyl 2-[(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl]piperidine-1-carboxylate (4.82 g, 9.30 mmol) and pyridine-3-boronic acid 1,3-propanediol cyclic ester (1.67 g, 10.2 mmol) were coupled according to the method described in Part F of Example 414. Palladium (II) acetate (0.0103 f, 0.046 mmol) was added as a solid. The reaction was heated for 15 hours. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 72:28) to provide 3.4 g of *tert*-butyl 2-{[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate as an off-white, crystalline solid.

Part D

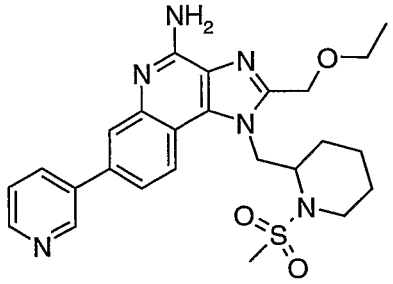
tert-Butyl 2-{[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]methyl}piperidine-1-carboxylate (3.15 g, 6.10 mmol) was deprotected according to the method described in Example 177 to provide 2.54 g of 2-ethoxymethyl-1-(piperidin-2-ylmethyl)-7-(pyridin-3-yl)-1*H*-

imidazo[4,5-*c*]quinolin-4-amine trihydrochloride as an off-white solid, mp >250 °C.

Anal. Calcd for $C_{24}H_{28}N_6O \cdot 3HCl \cdot 2H_2O$: C, 51.30; H, 6.28; N, 14.96. Found: C, 50.95; H, 6.38; N, 15.10.

Example 492

2-Ethoxymethyl-1-{[1-(methanesulfonyl)piperidin-2-yl]methyl}-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

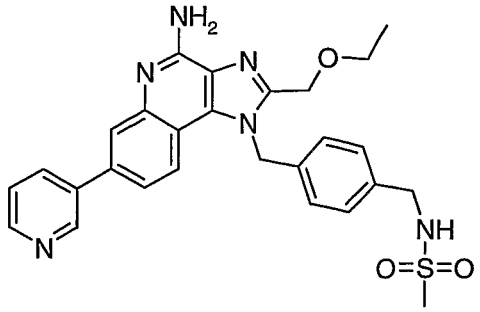


A solution of 2-ethoxymethyl-1-(piperidin-2-ylmethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine trihydrochloride (0.60 g, 1.1 mmol) and triethylamine (0.79 mL, 5.7 mmol) in chloroform (50 mL) was cooled to 4 °C. Methanesulfonyl chloride (0.12 mL, 1.5 mmol) was added, and the reaction was allowed to warm to ambient temperature and stirred overnight. Additional methanesulfonyl chloride (2.5 equivalents) was added at 4 °C over the course of several days. The work-up procedure described in Examples 178 to 181 was carried out. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from about 100:0 to 70:30) followed by recrystallization from acetonitrile to provide 0.19 g of 2-ethoxymethyl-1-{[1-(methanesulfonyl)piperidin-2-yl]methyl}-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 152-154 °C.

Anal. Calcd for $C_{25}H_{30}N_6O_3S \cdot 0.5\ H_2O$: C, 59.62; H, 6.20; N, 16.69. Found: C, 59.62; H, 6.44; N, 16.78.

Example 493

N-{4-[4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl] benzyl}methanesulfonamide



Part A

1-(*N*-BOC-aminomethyl)-4-(aminomethyl)benzene (5.0 g, 21 mmol) in dichloromethane (50 mL) was added dropwise to a mixture of 7-bromo-4-chloro-3-nitroquinoline (5.81 g, 20 mmol) and triethylamine (5.63 mL) in dichloromethane (60 mL). The reaction was stirred for 16 hours and then washed sequentially with water and saturated aqueous sodium chloride. The organic fraction was dried over sodium sulfate, filtered and concentrated to provide a yellow crystalline solid. Recrystallization from 2-propanol yielded 9.1 g of *tert*-butyl {4-[(7-bromo-3-nitroquinolin-4-ylamino)methyl]benzyl}carbamate as a yellow powder.

Part B

Ethyl viologen dibromide (0.069 g, 0.18 mmol), potassium carbonate (12.76 g, 92 mmol) in water (55mL), and sodium hydrosulfite (11.25 g, 65 mmol) in water (55mL) were added sequentially to a solution of *tert*-butyl {4-[(7-bromo-3-nitroquinolin-4-ylamino)methyl]benzyl}carbamate (9.0 g, 18.5 mmol) in dichloromethane (110 mL). The resulting biphasic mixture was stirred for 20 hours. The reaction was diluted with water (600 mL) and dichloromethane (500 mL). The layers were separated and the aqueous fraction was extracted with dichloromethane. The organic fractions were combined and washed sequentially with water and saturated aqueous sodium chloride. The organic fraction was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 8.5 g of *tert*-butyl {4-[(3-amino-7-bromoquinolin-4-ylamino)methyl]benzyl}carbamate as a yellow-brown amorphous solid.

Part C.

tert-Butyl {4-[(3-amino-7-bromoquinolin-4-ylamino)methyl]benzyl}carbamate (8.46 g, 18.5 mmol), triethylamine (2.25 mL)

and dichloromethane (92 mL) were combined. Ethoxyacetyl chloride (2.92 g, 24 mmol) was added dropwise to the mixture. The reaction was stirred for an additional 1.5 hours and then concentrated under reduced pressure. Ethanol (92 mL) and triethylamine (10.31 mL) were added to the residue and the reaction was heated at reflux temperature for 1.5 hours. A precipitate formed. The reaction was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed sequentially with water and saturated aqueous sodium chloride. The organic fraction was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. An initial purification by flash column chromatography eluting with a gradient of CMA in chloroform (2-10%) was followed by recrystallization from acetonitrile to provide 3.4 g of *tert*-butyl [4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl)benzyl]carbamate as yellow-orange crystals.

Part D

3-Chloroperoxybenzoic acid (2.91 g, 9.3 mmol, 55% pure) was added to a solution of *tert*-butyl [4-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl)benzyl]carbamate (3.2 g, 6.1 mmol) in chloroform (60 mL). The reaction was stirred for 1 hour and then cooled with an ice bath. Ammonium hydroxide (40 mL) was added and the reaction was stirred for 10 minutes. *p*-Toluenesulfonyl chloride (1.16 g, 6.1 mmol) was added in two portions. The cooling bath was removed and the mixture was stirred for an additional 16 hours. The layers were separated and the aqueous fraction was extracted with dichloromethane. The combined organic fractions were washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (CMA/chloroform) and subsequent recrystallization from acetonitrile yielded 1.15 g of *tert*-butyl [4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo [4,5-*c*]quinolin-1-ylmethyl)benzyl]carbamate as a tan solid.

Part E.

tert-Butyl [4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl) benzyl]carbamate (1.15 g, 2.1 mmol), triphenylphosphine

(0.005 g), pyridine-3-boronic acid 1,3-propanediol cyclic ester (0.365 g, 2.2 mmol), and *n*-propanol (3.67 mL) were combined. Aqueous sodium carbonate (2M, 1.12 mL) and water (0.6 mL) were added to the mixture and the flask was flushed with nitrogen. Palladium(II) acetate (0.0013 g) in toluene (0.200 mL) was added, and the flask was again flushed with nitrogen. The flask was sealed and heated in an oil bath at a temperature of 105 °C for 16 hours. The reaction was allowed to cool to room temperature and the mixture was diluted with dichloromethane and water. The layers were separated and the aqueous fraction was extracted with dichloromethane. The organic fractions were combined, washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography eluting with a gradient of CMA/chloroform and subsequent recrystallization from acetonitrile yielded 0.725 g of *tert*-butyl {4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl]benzyl}carbamate as flocculent white crystals, m.p. 195.5-197.0 °C.

Anal Calcd. for $C_{31}H_{34}N_6O_3$: %C, 69.13; %H, 6.36; %N, 15.60. Found: %C, 68.85; %H, 6.34; %N, 15.63.

Part F

tert-Butyl {4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl]benzyl}carbamate (0.660 g) was added to ethanolic hydrogen chloride (4M, 10 mL) and the solution was heated at reflux temperature for 30 minutes. The reaction was cooled to room temperature and concentrated under reduced pressure. Diethyl ether and water were added to the oily residue and the layers were separated. The aqueous fraction was brought to pH 13 with 10% aqueous sodium hydroxide and then extracted sequentially with dichloromethane and dichloromethane containing 5% methanol. The organic fractions were combined, washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 0.526 g of 1-(4-aminomethylbenzyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white solid, mp 211.0-213.5 °C.

Anal Calcd. for $C_{26}H_{26}N_6O$: %C, 71.21; %H, 5.98; %N, 19.16. Found: %C, 70.85; %H, 5.98; %N, 19.22.

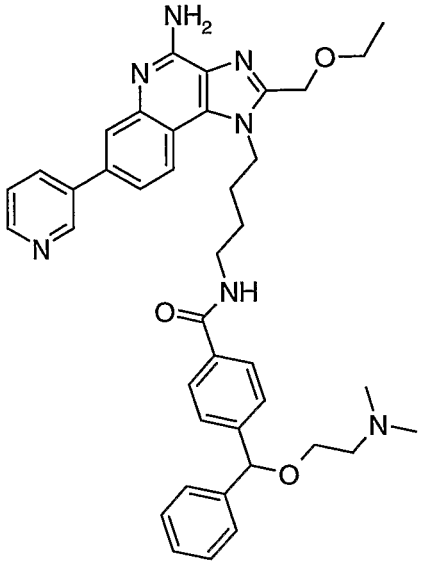
Part G.

Methanesulfonyl chloride (0.13 mL, 1.7 mmol) was added dropwise to a mixture of 1-(4-aminomethylbenzyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.520 g, 1.2 mmol) in dichloromethane (10 mL). The reaction was stirred for 16 hours and then saturated aqueous sodium carbonate was added. The layers were separated and the aqueous fraction was extracted with 95:5 chloroform/methanol. The organic fractions were combined and washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was purified by flash column chromatography with a gradient of CMA (2%-10%) in chloroform as the eluent. A final recrystallization from 2-propanol provided 0.240 g of *N*-{4-[4-amino-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-ylmethyl]benzyl}methanesulfonamide as white granular crystals, mp 228.0-229.0 °C.

Anal Calcd. for $C_{27}H_{28}N_6O_3S$: %C, 62.77; %H, 5.46; %N, 16.27; %S, 6.21. Found: %C, 62.55; %H, 5.13; %N, 16.15; %S, 6.11.

Example 494

N-[4-(4-Amino-2-ethoxymethyl-7-(pyridin-3-yl)imidazo[4,5-*c*]quinolin-1-yl)butyl]-4-[(2-dimethylaminoethoxy)phenylmethyl]benzamide



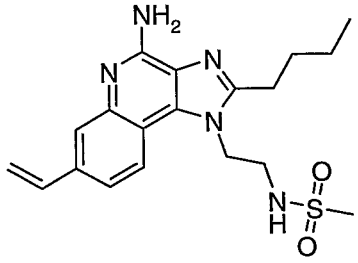
A mixture of 4-[(2-dimethylaminoethoxy)phenylmethyl]benzoic acid (0.433 g) and 1-hydroxybenzotriazole (0.196 g) in chloroform (7 mL) was cooled to 0 °C and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.277 g) was added in small portions over a 2 minute period. The mixture was stirred for 1 hour and then added dropwise to a chilled (0 °C) solution of 1-(4-aminobutyl)-2-ethoxymethyl-7-(pyridin-3-yl)-*1H*-imidazo[4,5-*c*]quinolin-4-amine (0.400 g) in anhydrous dimethylacetamide (7 mL). The cooling bath was removed and the reaction was stirred for an additional 16 hours. Water was added and the mixture was made acidic by the addition of 4N hydrochloric acid. The aqueous fraction was extracted with diethyl ether (3X) to remove the dimethylacetamide. Sodium hydroxide (10% in water) was added to make the aqueous fraction basic and the aqueous fraction was subsequently extracted with multiple portions of dichloromethane. The organic fractions were combined, washed sequentially with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using a gradient of CMA/chloroform as the eluent. A final recrystallization from acetonitrile provided 0.426 g of *N*-[4-(4-amino-2-ethoxymethyl-7-(pyridin-3-yl)imidazo[4,5-*c*]quinolin-1-yl)butyl]-4-[(2-

dimethylaminoethoxy)phenylmethyl]benzamide as a white crystalline solid, mp 157.0-161.0 °C.

Anal Calcd. for $C_{40}H_{45}N_7O_3 \bullet 1.0H_2O$: %C, 69.64; %H, 6.87; %N, 14.21. Found: %C, 69.81; %H, 7.07; %N, 14.25.

Example 495

N-[2-(4-Amino-2-butyl-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]methanesulfonamide



Part A

A solution of 7-bromo-4-chloro-3-nitroquinoline (143.8 g, 0.5 mol) in 800 mL warm DMF was added to a stirred solution of ethylenediamine in 200 mL DMF at room temperature; the reaction was stirred at room temperature overnight. The reaction was quenched with 2 L water and stirred for an additional hour. Additional water was added, and the mixture was stirred overnight. A precipitate formed and was isolated by filtration and air-dried overnight on the filter funnel to provide N^1-(7-bromo-3-nitroquinolin-4-yl)ethane-1,2-diamine as a yellow solid.

Part B

To a stirred solution of N^1-(7-bromo-3-nitroquinolin-4-yl)ethane-1,2-diamine (50 g, 0.167 mol) and triethylamine (2 equivalents) in 1500 mL dichloromethane, was slowly added methanesulfonic anhydride (1.2 equivalents), and the reaction was stirred overnight at room temperature. Water (1 L) was added, and the mixture was stirred vigorously for one hour. The organic layer was separated and concentrated under reduced pressure to provide *N*-[2-(7-bromo-3-nitroquinolin-4-ylamino)ethyl]methanesulfonamide.

Part C

An 8 L stainless steel Parr vessel was charged with *N*-[2-(7-bromo-3-nitroquinolin-4-ylamino)ethyl]methanesulfonamide (61 g), 5% Pt/C catalyst (6.0 g) and acetonitrile (3 L). The vessel was evacuated, filled with hydrogen (45 psi, 3.1 x 10^5 Pa), and shaken at ambient temperature overnight. The reaction mixture was filtered through CELITE filter agent and concentrated under reduced pressure to provide *N*-[2-(3-amino-7-bromoquinolin-4-ylamino)ethyl]methanesulfonamide.

Part D

To a stirred solution of *N*-[2-(3-amino-7-bromoquinolin-4-ylamino)ethyl]methanesulfonamide (46.4 g, 0.129 mol) in 1000 mL pyridine was slowly added valeryl chloride (1.1 equivalents). After 1.5 hours the mixture was yellow and turbid. The reaction mixture was then heated at reflux for 12 hours, allowed to cool to ambient temperature and concentrated under reduced pressure. The residue was mostly dissolved in 10% HCl to adjust to pH 1. The resulting suspension was adjusted to pH 12 with the addtion of 50% aqueous sodium hydroxide and stirred overnight. A precipitate formed and was isolated by filtration and air-dried to provide 45 g of *N*-[2-(7-bromo-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]methanesulfonamide as a pale gray/green solid.

Part E

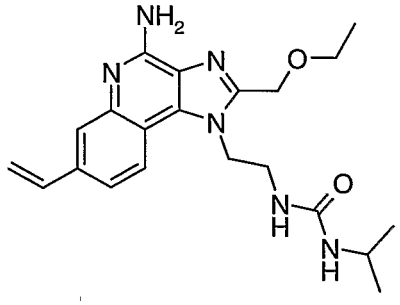
3-Chloroperoxybenzoic acid (1.0 equivalent of 50% pure material) was added to a solution of *N*-[2-(7-bromo-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]methanesulfonamide (44 g, 103.4 mmol) in 1000 mL dichloromethane. After 2 hours, concentrated ammonium hydroxide solution (600 mL) was added. The reaction was stirred for 15 minutes before *p*-toluenesulfonyl chloride (1.1 equivalents) was slowly added in small portions. The reaction was stirred overnight at room temperature and then water and potassium carbonate were added with vigorous stirring. A precipitate formed and was isolated by filtration to provide *N*-[2-(4-amino-7-bromo-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-ethyl]methanesulfonamide.

Part F

N-[2-(4-Amino-7-bromo-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]methanesulfonamide was coupled with potassium vinyltrifluoroborate according to the procedure described in Part D of Examples 440-455 and recrystallized from acetonitrile to provide *N*-[2-(4-amino-2-butyl-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]methanesulfonamide as an off-white solid.

Example 496

1-[2-(4-Amino-2-ethoxymethyl-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-3-(2-methylethyl)urea



Part A

A mixture of N^1-(7-bromo-3-nitroquinolin-4-yl)ethane-1,2-diamine (40 g, 0.129 mol), triethylamine (3.0 equivalents) and 1L dichloromethane was stirred vigorously as isopropyl isocyante (1.1 equivalents) was added dropwise. As the reaction progressed it became more homogeneous, and then a yellow precipitate formed. After 4 hours the volume of dichloromethane was reduced under reduced pressure. The yellow solid was isolated by filtration and air-dried overnight to provide 43 g 1-(2-methylethyl)-3-[2-(3-nitroquinolin-4-ylamino)ethyl]urea.

Part B

An 8L stainless steel Parr vessel was charged with 1-(2-methylethyl)-3-[2-(3-nitroquinolin-4-ylamino)ethyl]urea (44 g, 0.111 mol), 5% platinum on carbon (5 g) and acetonitrile (4000 mL). The vessel was evacuated, charged with hydrogen, and shaken vigorously for six hours. An analysis by HPLC and TLC indicated the reaction was not complete. Additional catalyst (5 g) was added, and the vessel was placed under hydrogen pressure and shaken overnight. The reaction mixture was filtered and concentrated under reduced pressure to

provide 1-[2-(3-amino-7-bromoquinolin-4-ylamino)ethyl]-3-(2-methylethyl)urea.

Part C

To a stirred solution of 1-[2-(3-amino-7-bromoquinolin-4-ylamino)ethyl]-3-(2-methylethyl)urea (27.2 g, 0.0743 mol) in 600 mL pyridine was slowly added ethoxyacetyl chloride (1.1 equivalents). After 1.5 hours the mixture was yellow and turbid. The reaction mixture was then heated at 80 °C for 12 hours and then concentrated under reduced pressure. The residue was dissolved in water and saturated aqueous potassium carbonate and stirred vigorously for three hours. A precipitate was present, was isolated by filtration, and air-dried for 48 hours to provide 32 g of 1-[2-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-3-(2-methylethyl)urea.

Part D

The method described in Part E of Example 495 was used to oxidize and aminate 1-[2-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-3-(2-methylethyl)urea (31 g, 71.4 mmol). The isolated product was recrystallized from acetonitrile to provide 1-[2-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-c]quinolin-1-yl)ethyl]-3-(2-methylethyl)urea.

Part E

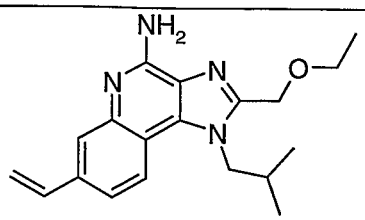
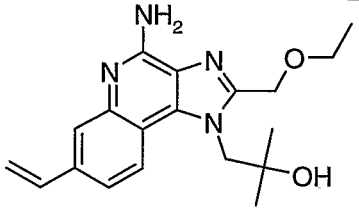
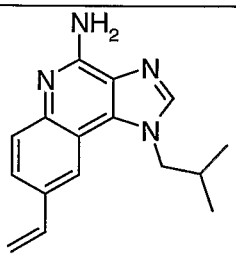
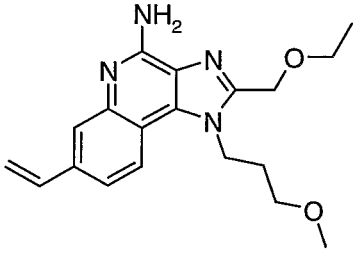
1-[2-(4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-c]quinolin-1-yl)ethyl]-3-(2-methylethyl)urea was coupled with potassium vinyltrifluoroborate according to the procedure described in Part D of Examples 440-455 to provide *N*-[2-(4-amino-2-butyl-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-3-(2-methylethyl)urea as an off-white solid.

MS (APCI) *m/z* 397.2 $(M + H)^+$.

Examples 497-500

The bromide starting material indicated in the table below was coupled with potassium vinyltrifluoroborate according to the procedure described in Part D of Examples 440-463 and recrystallized from acetonitrile to provide the products shown in the table below.

Examples 497-500

Example	Starting Material	Product Structure
497	7-Bromo-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	
498	1-[4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	
499	8-Bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	
500	7-Bromo-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	

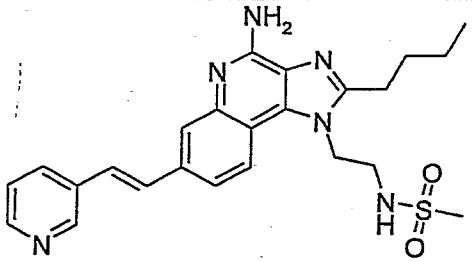
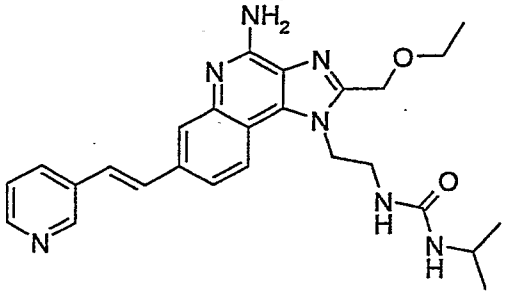
Example	Product Name	Form	MS (APCI) *m/z* $(M+H)^+$	Anal.
497	2-Ethoxymethyl-1-(2-methylpropyl)-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white solid	325.1	Calcd for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.46; N, 17.27. Found: C, 69.99; H, 7.60; N, 17.36.

498	1-[4-Amino-2-ethoxymethyl-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	Off-white solid	341.1	Calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46. Found: C, 66.09; H, 7.41; N, 16.16.
499	1-(2-Methylpropyl)-8-vinyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white solid	267.2	Not measured
500	2-Ethoxymethyl-1-(3-methoxypropyl)-7-vinyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-white solid	341.1	Not measured

Examples 501-506

The method described in Part E of Example 440-455 was used to couple the vinyl compound indicated in the table below with 3-bromopyridine to provide the product shown and named in the table below.

Example 501-506

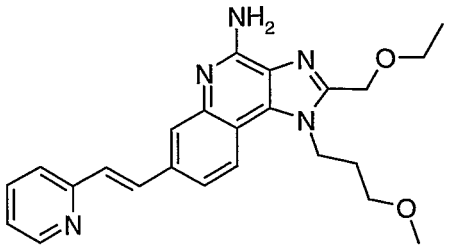
Example	Starting Vinyl Compound	Product Structure	Product Name	Form	MS (APCI) m/z (M+H)+
501	Example 495		*(E)*-*N*-{2-[4-Amino-2-butyl-7-(2-pyridin-3-ylvinyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}methanesulfonamide	Off-White solid	465.0
502	Example 496		*(E)*-*N*-{2-[4-Amino-2-ethoxymethyl-7-(2-pyridin-3-ylvinyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N*'-(2-methylethyl)urea	Off-White solid	474.1

503	Example 497		*(E)*-2-Ethoxymethyl-1-(2-methylpropyl)-7-(2-pyridin-3-ylvinyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-White solid	402.2
504	Example 498		*(E)*-1-[4-Amino-2-ethoxymethyl-7-(2-pyridin-3-ylvinyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol	Off-White solid	418.1
505	Example 499		*(E)*-1-(2-Methylpropyl)-8-(2-pyridin-3-ylvinyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Off-White solid	344.0

506	Example 500		*(E)*-2-Ethoxymethyl-1-(3-methoxypropyl)-7-(2-pyridin-3-ylvinyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine	Not reported	418.0

Example 507

(E)-2-Ethoxymethyl-1-(3-methoxypropyl)-7-(2-pyridin-2-ylvinyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



A thick walled glass tube, equipped with magnetic stir-bar, was charged with toluene (20 mL/g), palladium (II) acetate (0.1 equivalents), tri-*ortho*-tolylphosphine (0.3 equivalents), triethylamine (3.0 equivalents), 2-vinylpyridine (1.0 equivalent), and 7-bromo-2-ethoxymethyl-1-(3-methoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.0 eq.). The tube was purged with nitrogen and sealed. The reaction mixture was heated at 120 °C for 24-48 hours. The reaction mixture was allowed to cool and then concentrated under reduced pressure. The solid residue was partitioned between dichloromethane and water, and the mixture was adjusted to pH 12 with the addition of 10% aqueous sodium hydroxide. The organic layer was separated and purified by flash chromatography on silica gel (eluting with chloroform:methanol in a gradient from 100:0 to 90:10) followed by recrystallization from acetonitrile to provide *(E)*-2-ethoxymethyl-1-(3-methoxypropyl)-7-(2-pyridin-2-ylvinyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white solid.

MS (APCI) *m/z* 418.2 $(M+H)^+$.

Examples 508-557

Part A

Concentrated hydrochloric acid (~15 mL) was added to a suspension of *tert*-butyl [4-(4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate (3.19 g, 6.7 mmol) in ethanol (6.4 mL), and the reaction was

stirred for 30 minutes. The reaction was adjusted to pH 13 with the addition of 50% aqueous sodium hydroxide. A precipitate formed, was isolated by filtration, washed with 1% sodium carbonate, and dried overnight on the filter funnel to provide 1-(4-aminobutyl)-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine, which contained some water.

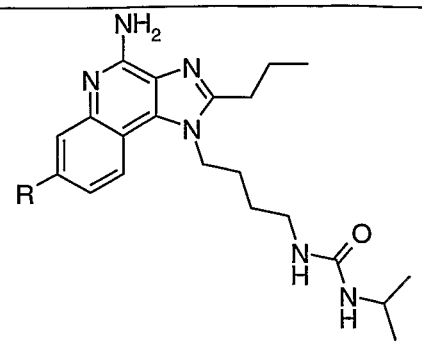
Part B

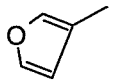
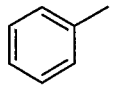
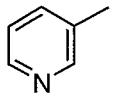
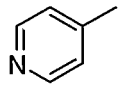
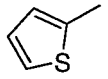
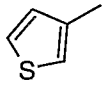
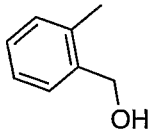
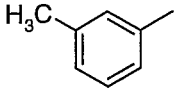
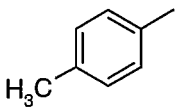
A suspension of 1-(4-aminobutyl)-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.00 g, 5.3 mmol) in chloroform (20 mL) was cooled to 0 °C, and a solution of isopropyl isocyanate (5.3 mmol) in chloroform (3 mL/g) was added slowly over a period of eight minutes. After one hour, additional isopropyl isocyanate (0.53 mmol) in chloroform was added. Additional isopropyl isocyanate (2.15 mmol) was added again after an additional 2.5 hours. A precipitate was present and was isolated by filtration, washed with cold chloroform, and dried overnight on the filter funnel to provide 1.99 g of *N*-{4-[4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-(1-methylethyl)urea as a white solid.

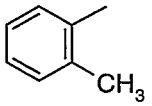
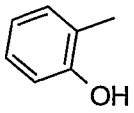
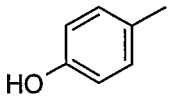
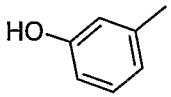
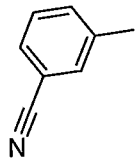
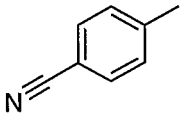
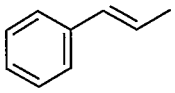
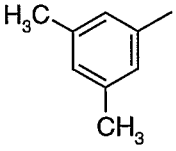
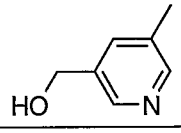
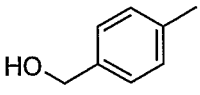
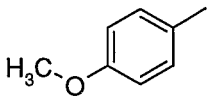
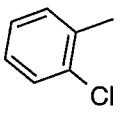
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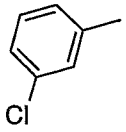
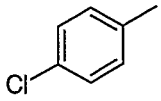
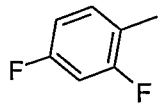
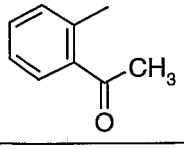
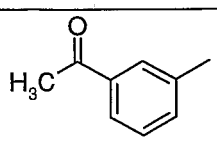
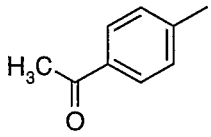
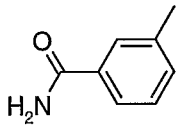
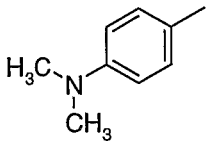
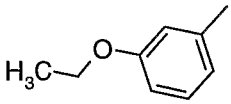
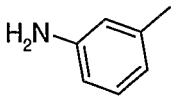
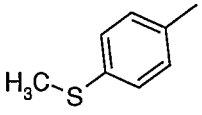
N-{4-[4-Amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-(1-methylethyl)urea was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

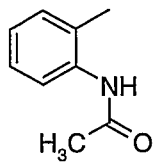
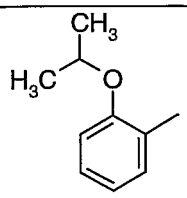
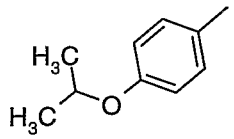
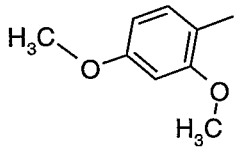
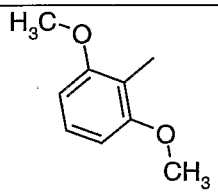
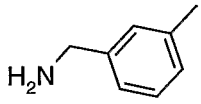
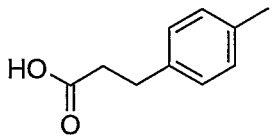
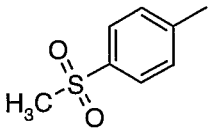
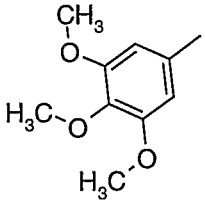
Examples 508-557

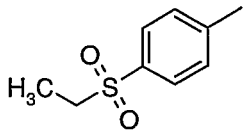
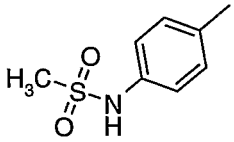
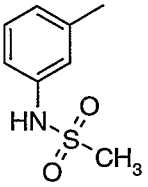
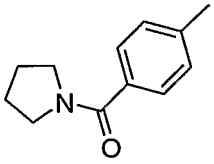
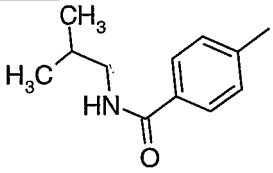
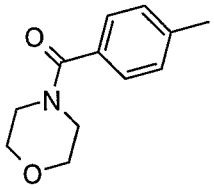
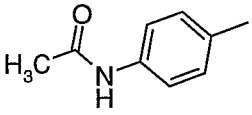
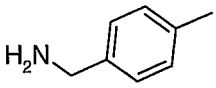
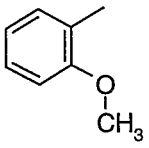


Example	R	Measured Mass (M+H)
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509		459.2888
510		460.2821
511		460.2820
512		465.2428
513		465.2402
514		489.3017
515		473.3035
516		473.3037

517		473.3009
518		475.2831
519		475.2809
520		475.2786
521		484.2824
522		484.2817
523		485.3011
524		487.3150
525		490.2932
526		489.2955
527		489.2944
528		493.2472

529		493.2459
530		493.2487
531		495.2691
532		501.2973
533		501.2957
534		501.2982
535		502.2921
536		502.3275
537		503.3109
538		474.2977
539		505.2754

540		516.3057
541		517.3257
542		517.3261
543		519.3101
544		519.3092
545		488.3139
546		531.3060
547		537.2693
548		549.3190

549		551.2814
550		552.2754
551		552.2759
552		556.3423
553		558.3538
554		572.3351
555		516.3045
556		488.3117
557		489.2997

Examples 558-582

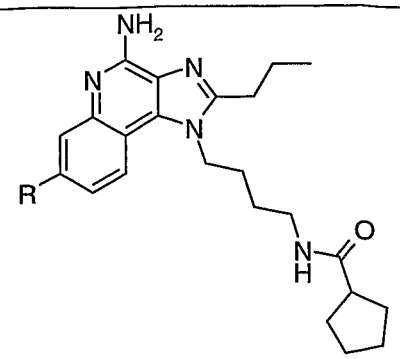
Part A

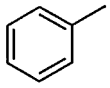
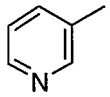
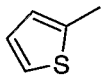
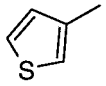
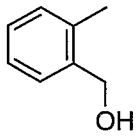
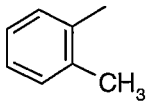
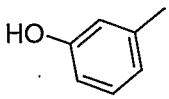
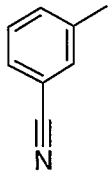
A suspension of 1-(4-aminobutyl)-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.42 g, 6.4 mmol) and triethylamine (0.99 mL, 7.1 mmol) in chloroform (240 mL) was cooled to 0 °C, and cyclopentanecarbonyl chloride (0.78 mL, 6.4 mmol) was added dropwise over a period of five minutes. The reaction was stirred for ten minutes, washed sequentially with water (50 mL) and 1% aqueous sodium carbonate (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was triturated with isopropanol:water (10 mL/g and 1.7 mL/g) and isolated by filtration. The filtrate was concentrated under reduced pressure and recrystallized from isopropanol (5 mL/g). The two solids were combined and dried overnight in a vacuum oven to provide 1.51 g of *N*-{4-[4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide as a light yellow solid.

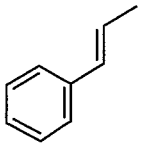
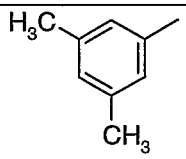
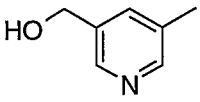
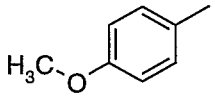
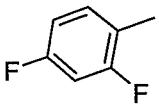
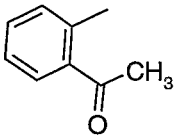
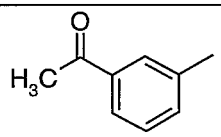
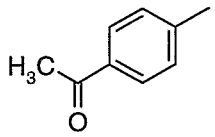
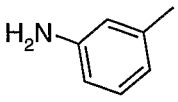
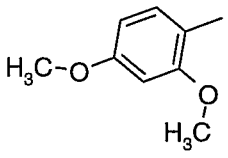
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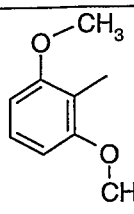
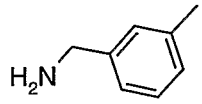
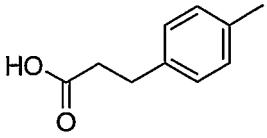
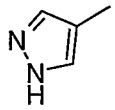
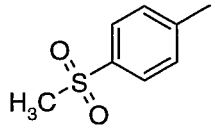
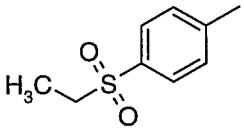
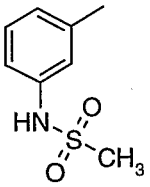
N-{4-[4-Amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-cyclopentanecarboxamide was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 558-582



Example	R	Measured Mass (M+H)
558		470.2917
559		471.2877
560		476.2485
561		476.2503
562		500.3024
563		484.3093
564		486.2841
565		495.2852

566		496.3090
567		498.3227
568		501.2946
569		500.3015
570		506.2754
571		512.3023
572		512.2994
573		512.3024
574		485.3015
575		530.3084

576		530.3101
577		499.3166
578		542.3149
579		460.2821
580		548.2672
581		562.2844
582		563.2784

Examples 583-611

Part A

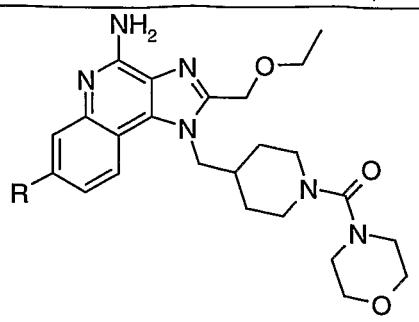
A solution of 7-bromo-2-ethoxymethyl-1-(piperidin-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride (4.0 g, 8.1 mmol) and triethylamine (5.67 mL, 40.7 mmol) in chloroform (300 mL) was cooled to 0 °C, and 4-morpholinecarbonyl chloride (0.95 mL, 8.1 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred overnight before it was diluted with chloroform (200 mL); washed sequentially with water (200 mL), 2 M sodium carbonate (2 x 200 mL), water (200 mL), and brine (200 mL); and concentrated under reduced pressure. The residue was triturated with ethyl acetate and subsequently recrystallized from acetonitrile to provide 3.64 g of 7-bromo-2-ethoxymethyl-1-{[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 198-199 °C.

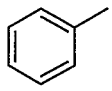
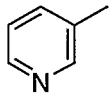
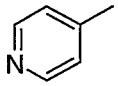
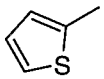
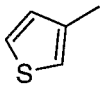
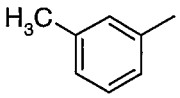
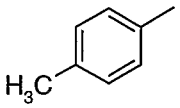
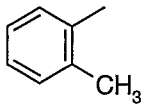
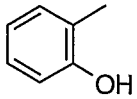
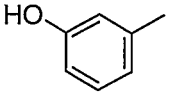
Anal. Calcd for $C_{24}H_{31}BrN_6O_3$: C, 54.24; H, 5.88; N, 15.81. Found: C, 54.27; H, 5.64; N, 15.87.

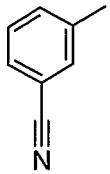
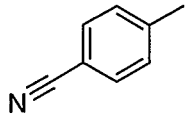
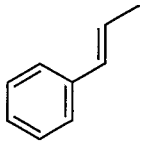
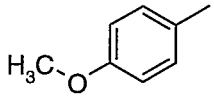
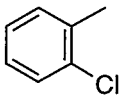
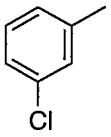
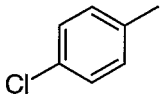
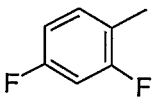
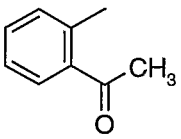
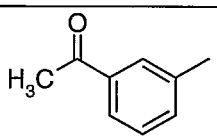
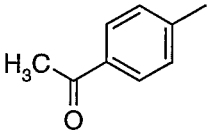
Part B

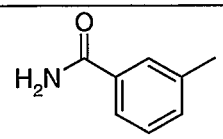
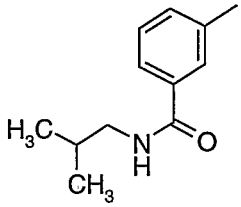
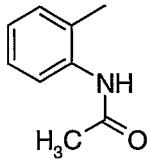
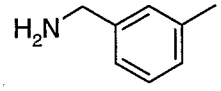
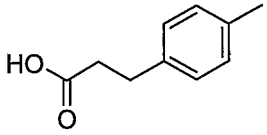
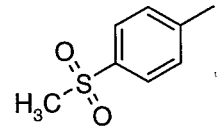
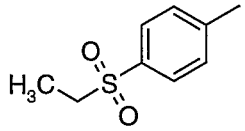
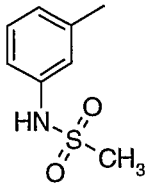
7-Bromo-2- ethoxymethyl-1-{[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 583-611



Example	R	Measured Mass (M+H)
583		529.2931
584		530.2852
585		530.2841
586		535.2465
587		535.2465
588		543.3043
589		543.3057
590		543.3105
591		545.2865
592		545.2874

593		554.2842
594		554.2849
595		555.3068
596		559.3006
597		563.2570
598		563.2519
599		563.2496
600		565.2722
601		571.3003
602		571.3016
603		571.3063

604		572.2994
605		628.3633
606		586.3104
607		558.3211
608		601.3146
609		607.2709
610		621.2830
611		622.2778

Examples 612-642

Part A

Hydrogen chloride (100 mL of a 4 M solution in 1,4-dioxane) was added to *tert*-butyl [4-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]carbamate (10.0 g, 20.3 mmol), and the reaction was stirred for one hour. The reaction was adjusted to pH 11 with the addition of sodium hydroxide pellets in a small amount of water. Chloroform (300 mL) was added followed by saturated aqueous sodium bicarbonate (50 mL). The organic layer was separated, dried over sodium sulfate, filtered, concentrated under reduced pressure, and dried overnight in a drying oven to provide 5.60 g of 1-(4-aminobutyl)-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a light yellow solid.

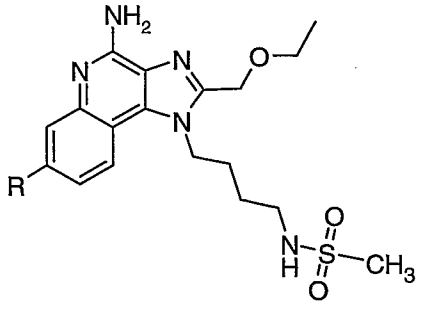
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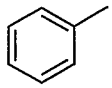
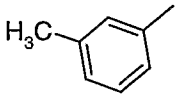
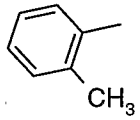
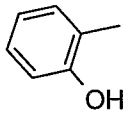
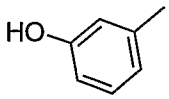
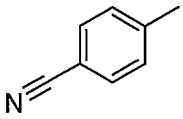
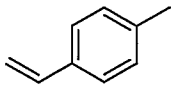
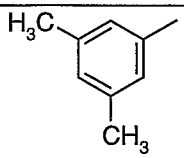
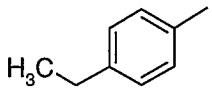
Methanesulfonyl chloride (0.44 mL, 5.7 mmol) was added to a suspension of 1-(4-aminobutyl)-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.04 g, 5.2 mmol) and triethylamine (0.94 mL, 6.8 mmol) in chloroform (100 mL), and the reaction was stirred for four hours. Water was added; a precipitate formed. The aqueous layer was adjusted to pH 10 with the addition of 50% aqueous sodium hydroxide. The precipitate was isolated by filtration, washed with cold chloroform, and dried overnight on the filter funnel. Material from another run was added, and entire procedure was repeated to eliminate unreacted starting material. *N*-{4-[4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide (2.95 g) was obtained as a white solid.

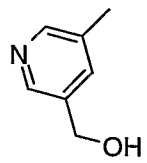
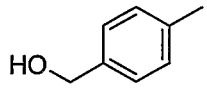
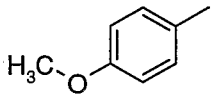
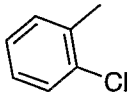
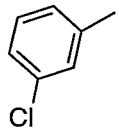
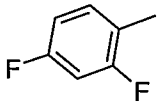
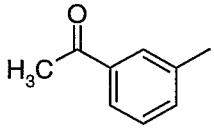
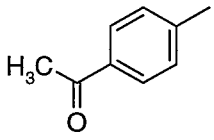
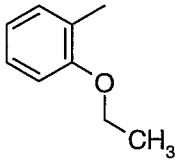
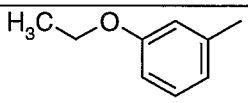
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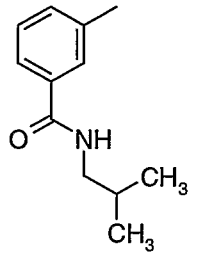
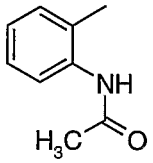
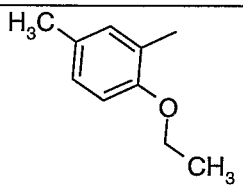
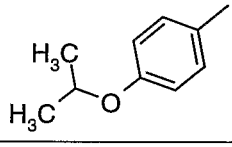
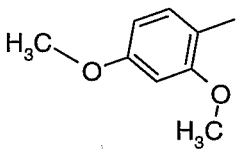
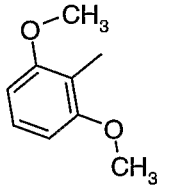
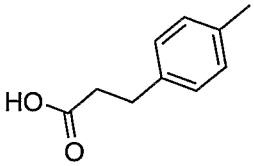
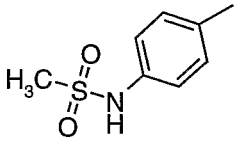
N-{4-[4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

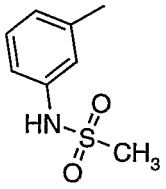
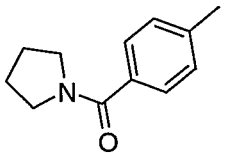
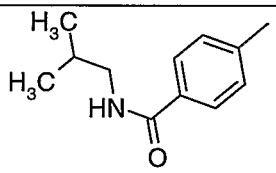
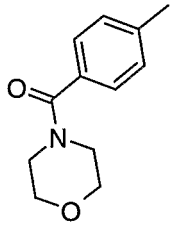
Examples 612-642



Example	R	Measured Mass (M+H)
612		468.2072
613		482.2245
614		482.2243
615		484.2014
616		484.2051
617		493.2035
618		494.2239
619		496.2400
620		496.2396

621		499.2145
622		498.2190
623		498.2167
624		502.1650
625		502.1717
626		504.1894
627		510.2177
628		510.2184
629		512.2349
630		512.2345

631		567.2750
632		525.2305
633		526.2516
634		526.2512
635		528.2282
636		528.2320
637		540.2274
638		561.1957

639		561.1987
640		565.2621
641		567.2791
642		581.2590

Example 643-663

Part A

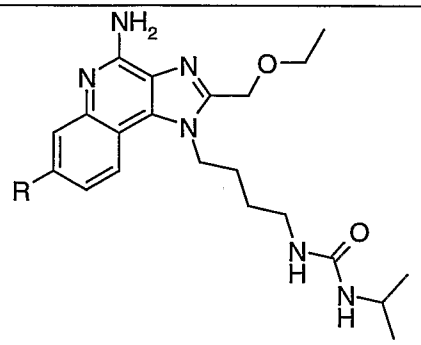
A solution of 1-(4-aminobutyl)-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.00 g, 5.1 mmol) in chloroform (36 mL) was cooled to 0 °C, and a cold solution of isopropyl isocyanate (0.50 mL, 5.4 mmol) in chloroform (4 mL) was added slowly. A precipitate formed, and the reaction was stirred for 45 minutes. The reaction mixture was triturated with ethyl acetate (200 mL), and the precipitate was isolated by filtration and dried for three days in a drying oven to provide 1.86 g of *N*-{4-[4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-(1-methylethyl)urea as a white solid, mp 211 °C.

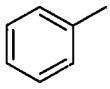
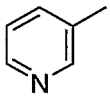
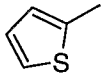
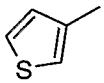
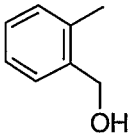
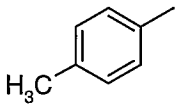
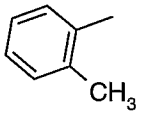
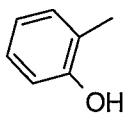
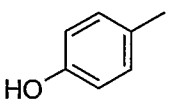
Anal. Calcd for $C_{21}H_{29}BrN_6O_2$: C, 52.83; H, 6.12; N, 17.60. Found: C, 52.52; H, 6.13; N, 17.29.

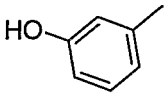
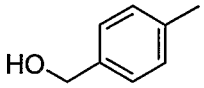
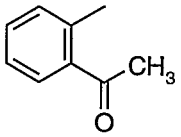
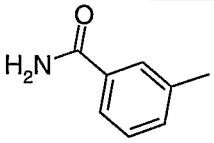
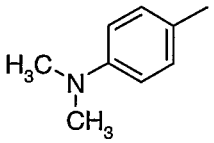
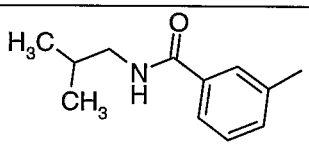
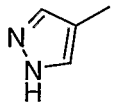
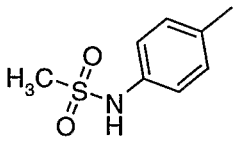
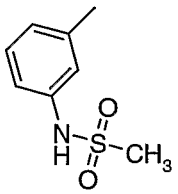
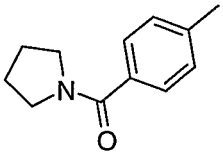
Part B

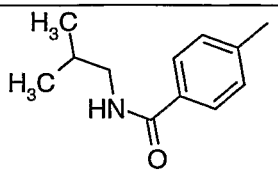
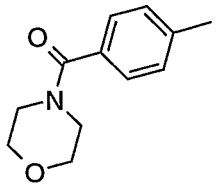
N-{4-[4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-*N'*-(1-methylethyl)urea was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

Example 643-663



Example	R	Measured Mass (M+H)
643		475.2793
644		476.2749
645		481.2385
646		481.2366
647		505.2915
648		489.2940
649		489.2956
650		491.2746
651		491.2772

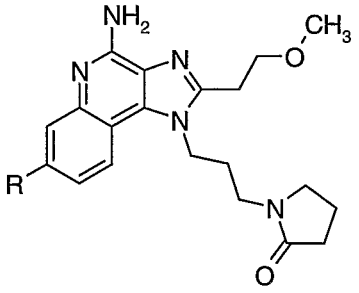
652		491.2758
653		505.2906
654		517.2902
655		518.2886
656		518.3214
657		574.3497
658		465.2721
659		568.2730
660		568.2715
661		572.3354

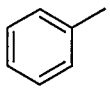
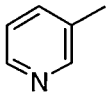
662		574.3502
663		588.3318

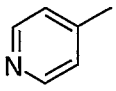
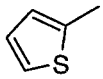
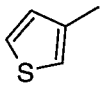
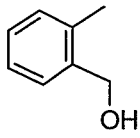
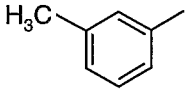
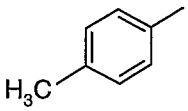
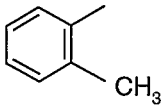
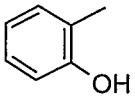
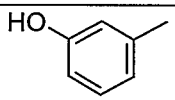
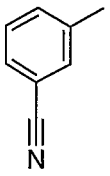
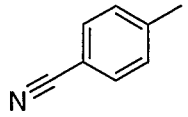
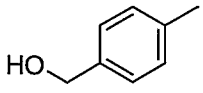
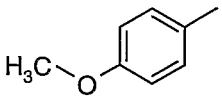
Examples 664-703

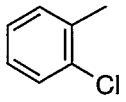
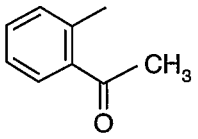
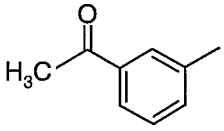
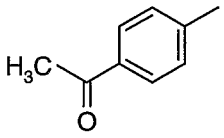
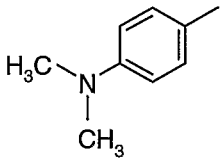
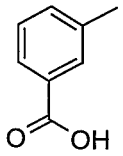
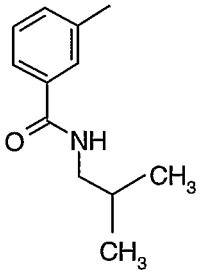
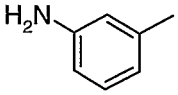
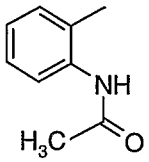
1-{3-[4-Amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

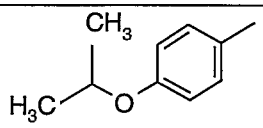
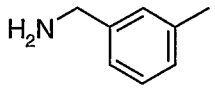
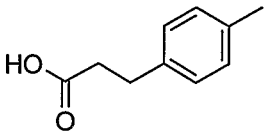
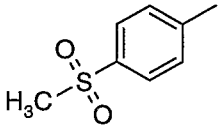
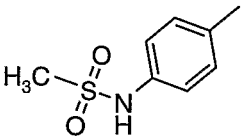
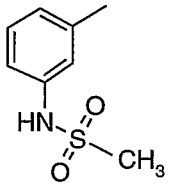
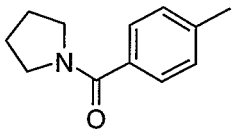
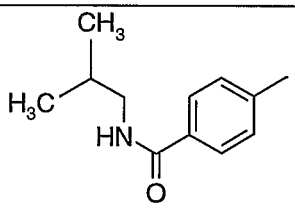
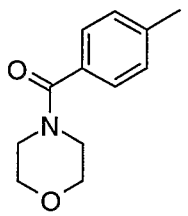
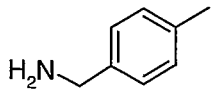
Examples 664-703

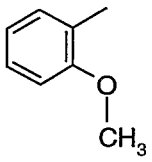
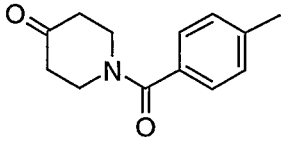
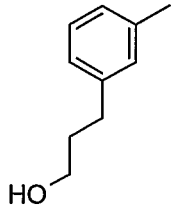
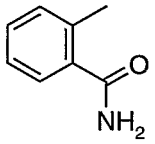
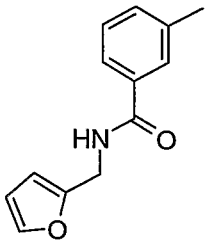
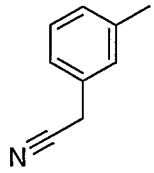


Example	R	Measured Mass (M+H)
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665		445.2348

666		445.2376
667		450.1961
668		450.1949
669		474.2487
670		458.2561
671		458.2533
672		458.2528
673		460.2343
674		460.2322
675		469.2308
676		469.2344
677		474.2486
678		474.2510

679		478.1996
680		486.2490
681		486.2463
682		486.2488
683		487.2797
684		488.2299
685		543.3068
686		459.2486
687		501.2592

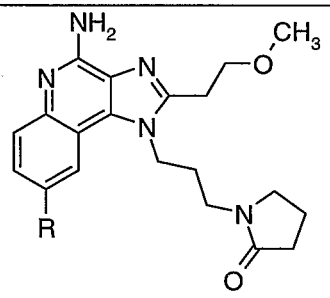
688		502.2805
689		473.2643
690		516.2563
691		522.2159
692		537.2263
693		537.2266
694		541.2872
695		543.3067
696		557.2853
697		473.2643

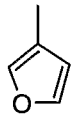
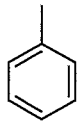
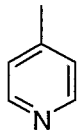
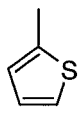
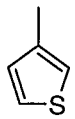
698		474.2495
699		569.2845
700		502.2812
701		487.2454
702		567.2703
703		483.2511

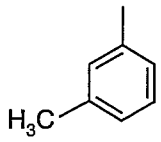
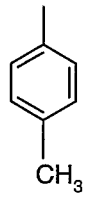
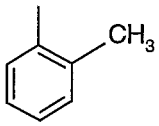
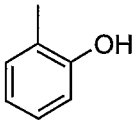
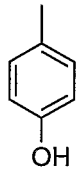
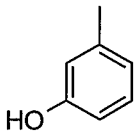
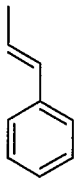
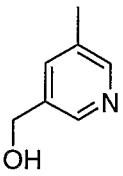
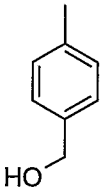
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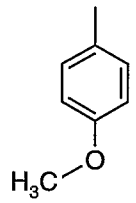
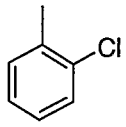
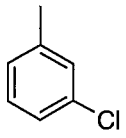
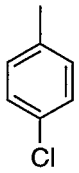
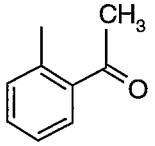
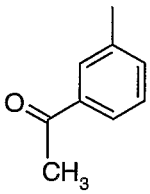
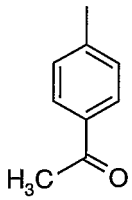
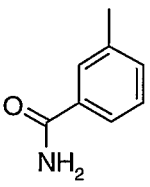
1-{3-[4-Amino-8-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}pyrrolidin-2-one was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

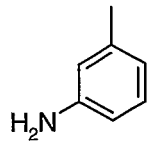
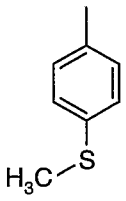
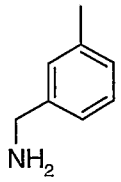
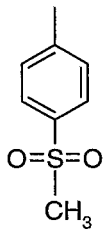
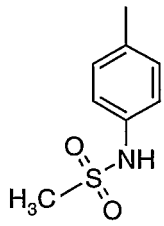
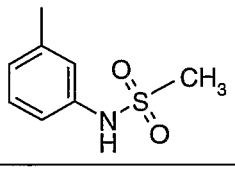
Examples 704-738

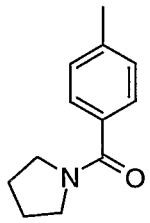
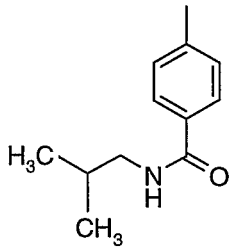
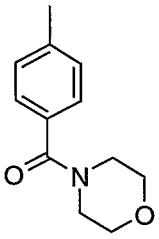
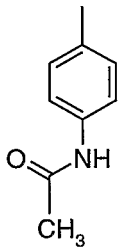
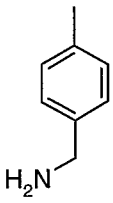
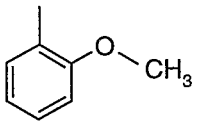


Example	R	Measured Mass (M+H)
704		434.2216
705		444.2412
706		445.2380
707		450.1968
708		450.1963

709		458.2571
710		458.2547
711		458.2563
712		460.2370
713		460.2324
714		460.2359
715		470.2581
716		475.2460
717		474.2530

718		474.2484
719		478.2023
720		478.2005
721		478.1989
722		486.2513
723		486.2530
724		486.2545
725		487.2502

726		459.2529
727		490.2287
728		501.2592
729		473.2639
730		522.2183
731		537.2275
732		537.2269

733		541.2952
734		543.3086
735		557.2878
736		501.2599
737		473.2668
738		474.2533

Example 739-762

Part A

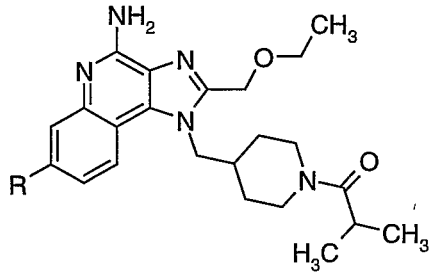
A solution of 7-bromo-2-ethoxymethyl-1-(piperidin-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride (4.0 g, 8.1 mmol) and triethylamine (5.67 mL, 40.7 mmol) in chloroform (300 mL) was treated with isobutyryl chloride (0.85 mL, 8.1 mmol) according to the method described in Part A of Examples 583-611. The reaction was complete after one hour. Following trituration with ethyl acetate, the solid was recrystallized from ethyl acetate and then triturated with hot acetonitrile and isolated by filtration to provide 3.63 g of 7-bromo-2-ethoxymethyl-1-{[1-(2-methylpropylcarbonyl)piperidin-4-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid, mp 199-200 °C.

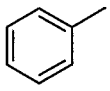
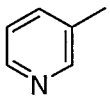
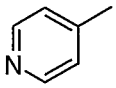
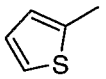
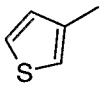
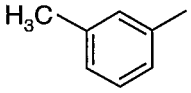
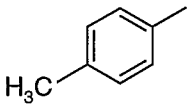
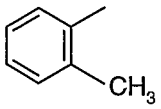
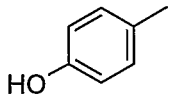
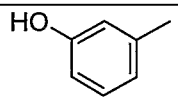
Anal. Calcd for $C_{23}H_{30}BrN_5O_2$: C, 56.56; H, 6.19; N, 14.34. Found: C, 56.49; H, 6.33; N, 14.12.

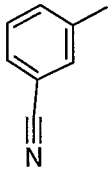
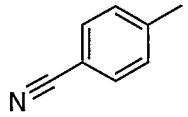
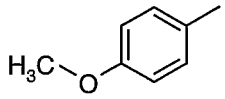
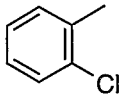
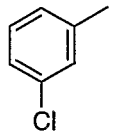
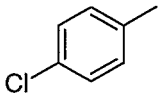
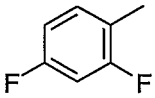
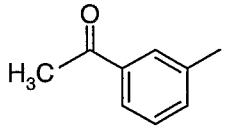
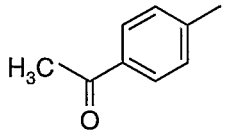
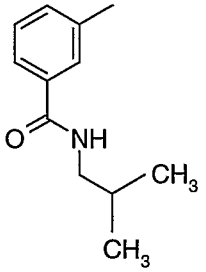
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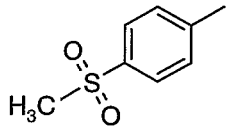
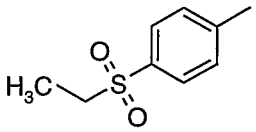
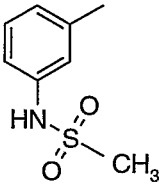
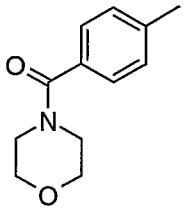
7-Bromo-2-ethoxymethyl-1-{[1-(2-methylpropylcarbonyl)piperidin-4-yl]methyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

Example 739-762



Example	R	Measured Mass (M+H)
739		486.2873
740		487.2845
741		487.2839
742		492.2446
743		492.2407
744		500.3025
745		500.3015
746		500.3022
747		502.2812
748		502.2826

749		511.2816
750		511.2824
751		516.3008
752		520.2502
753		520.2512
754		520.2506
755		522.2695
756		528.2963
757		528.2943
758		585.3572

759		564.2650
760		578.2791
761		579.2740
762		599.3309

Examples 763-785

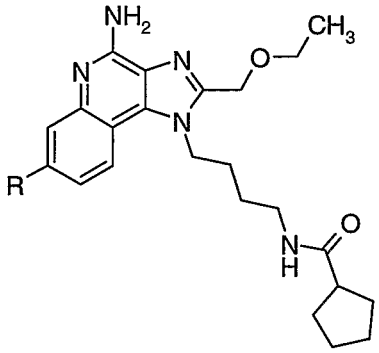
Part A

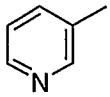
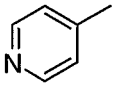
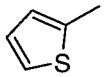
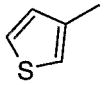
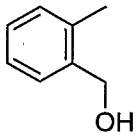
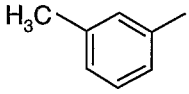
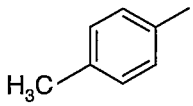
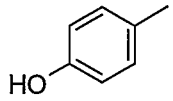
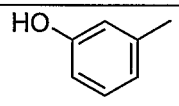
Cyclopentanecarbonyl chloride (0.80 mL, 6.6 mmol) was added dropwise over a period of five minutes to a suspension of 1-(4-aminobutyl)-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.00 g, 5.1 mmol) and triethylamine (0.78 mL, 5.6 mmol) in chloroform (200 mL). The reaction was stirred for 2.5 hours and then stored for three days in a refrigerator. Additional cyclopentanecarbonyl chloride (0.18 mL) was added, and the reaction was stirred for 30 minutes and treated as described for Examples 558-583. The crude product was recrystallized from isopropanol (13 mL/g), isolated by filtration, and dried overnight on the filter funnel to provide 1.60 g of *N*-{4-[4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide as a white solid.

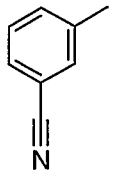
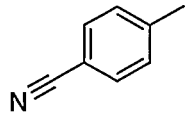
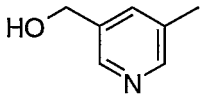
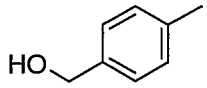
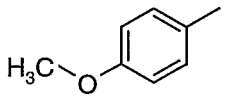
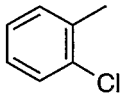
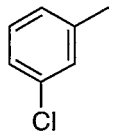
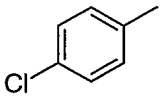
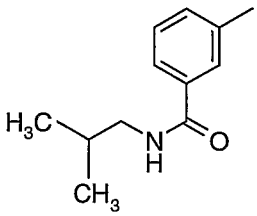
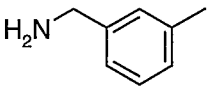
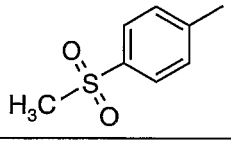
Part B

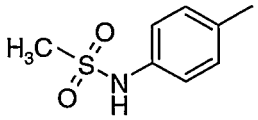
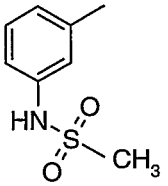
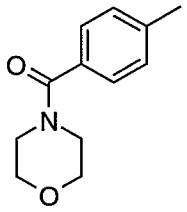
N-{4-[4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-cyclopentanecarboxamide was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 763-785



Example	R	Measured Mass (M+H)
763		487.2841
764		487.2839
765		492.2468
766		492.2411
767		516.3013
768		500.3054
769		500.3050
770		502.2824
771		502.2812

772		511.2804
773		511.2807
774		517.2941
775		516.3018
776		516.2982
777		520.2447
778		520.2510
779		520.2469
780		585.3587
781		515.3151
782		564.2663

783		579.2753
784		579.2776
785		599.3339

Example 786-806

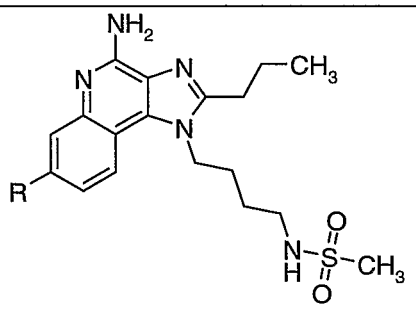
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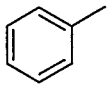
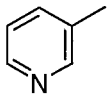
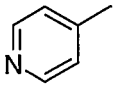
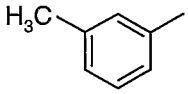
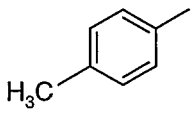
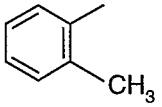
A suspension of 1-(4-aminobutyl)-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3.27 g, 8.7 mmol) and triethylamine (3.82 mL, 11.3 mmol) in chloroform (165 mL) was cooled to 0 °C. A cold solution of methanesulfonyl chloride (1.37 mL, 9.6 mmol) in chloroform (10 mL) was slowly added. The reaction was allowed to warm to ambient temperature after 15 minutes. Additional triethylamine (3.74 mL) and methanesulfonyl chloride (2.12 mL) were added over the course of several days to drive the reaction to completion. The reaction was concentrated under reduced pressure, and the residue was partitioned between 1% aqueous sodium carbonate and chloroform. The aqueous layer was adjusted to pH 13 with the addition of saturated aqueous sodium bicarbonate and 50% aqueous sodium hydroxide. The precipitate was isolated by filtration, air-dried, and combined with material from another run. The crude product was recrystallized from isopropanol:water (15 mL/g:1.5 mL/g) and dried in a drying oven for several days to provide 1.48 g of *N*-{4-[4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide as a white solid.

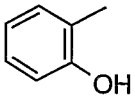
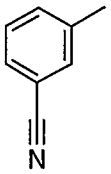
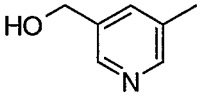
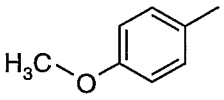
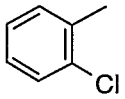
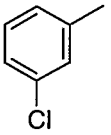
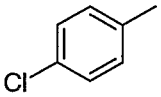
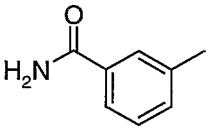
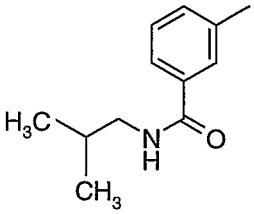
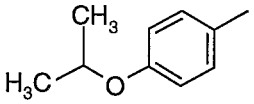
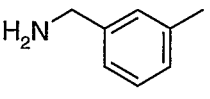
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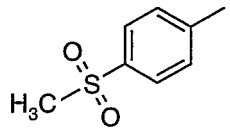
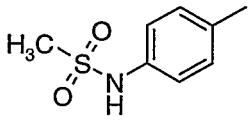
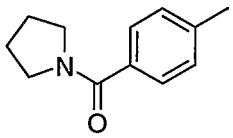
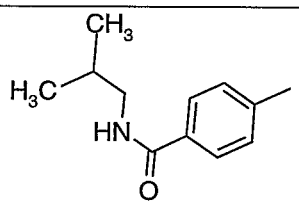
N-{4-[4-Amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 786-806



Example	R	Measured Mass (M+H)
786		452.2107
787		453.2040
788		453.2061
789		466.2274
790		466.2247
791		466.2280

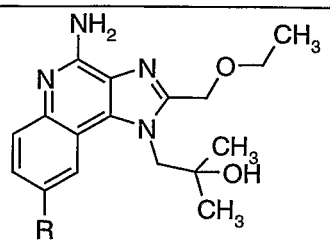
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793		477.2056
794		483.2149
795		482.2186
796		486.1711
797		486.1713
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799		495.2148
800		551.2762
801		510.2527
802		481.2388

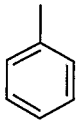
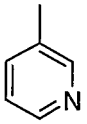
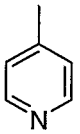
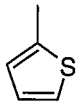
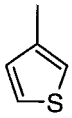
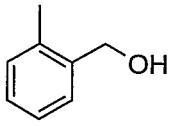
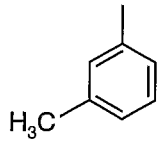
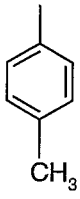
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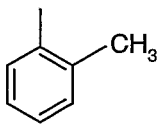
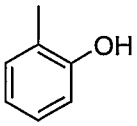
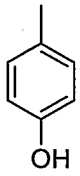
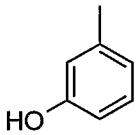
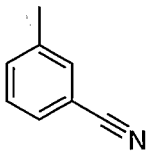
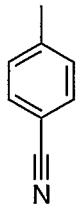
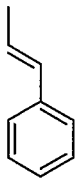
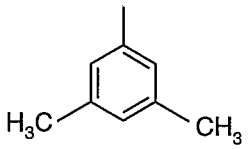
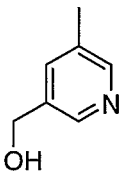
Examples 807-860

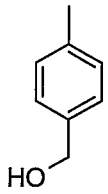
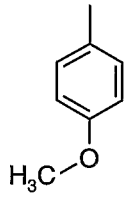
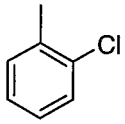
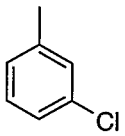
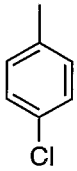
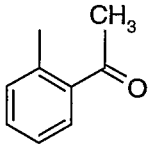
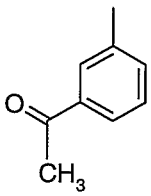
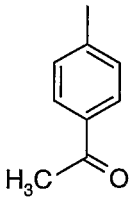
1-(4-Amino-8-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

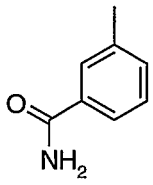
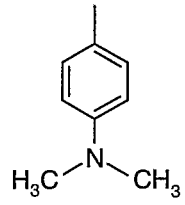
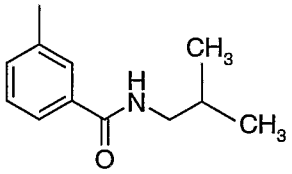
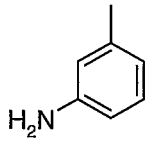
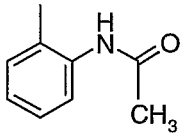
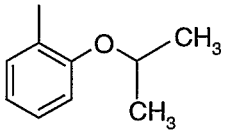
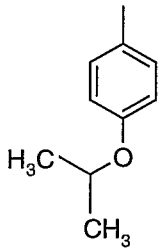
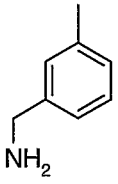
Example 807-860

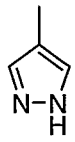
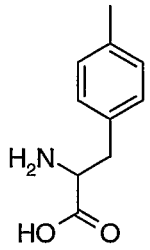
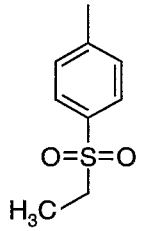
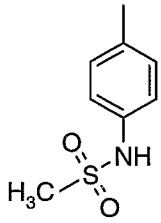
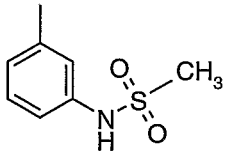
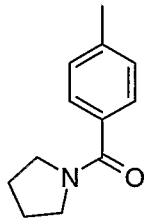
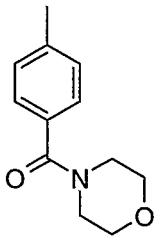


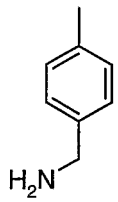
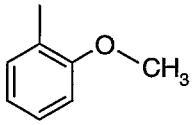
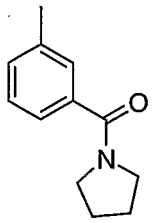
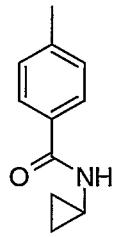
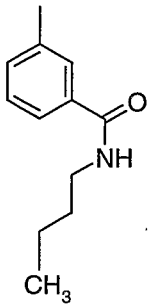
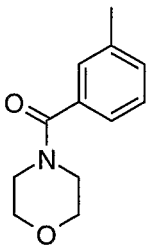
Example	R	Measured Mass (M+H)
807		391.2158
808		392.2117
809		392.2101
810		397.1702
811		397.1716
812		421.2254
813		405.2313
814		405.2303

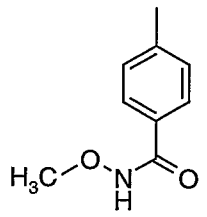
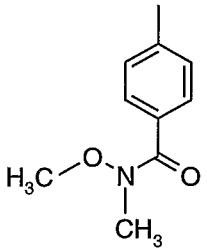
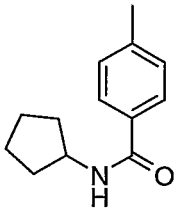
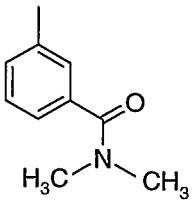
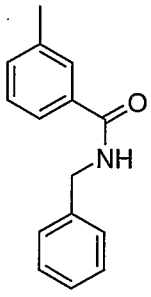
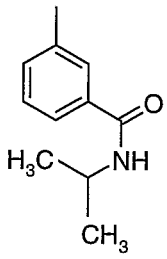
815		405.2323
816		407.2123
817		407.2115
818		407.2117
819		416.2117
820		416.2068
821		417.2311
822		419.2468
823		422.2206

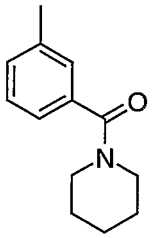
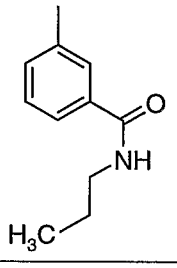
824		421.2281
825		421.2275
826		425.1750
827		425.1758
828		425.1772
829		433.2227
830		433.2268
831		433.2265

832		434.2209
833		434.2561
834		490.2814
835		406.2247
836		448.2364
837		449.2564
838		449.2574
839		420.2432

840		381.2046
841		478.2410
842		483.2058
843		484.2024
844		484.2026
845		488.2686
846		504.2607

847		420.2394
848		421.2247
849		488.2662
850		474.2520
851		490.2816
852		504.2585

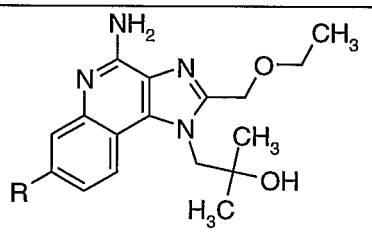
853		464.2324
854		478.2449
855		502.2843
856		462.2492
857		524.2639
858		476.2647

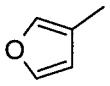
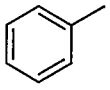
859		502.2809
860		476.2672

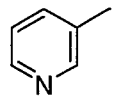
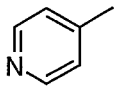
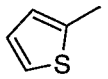
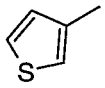
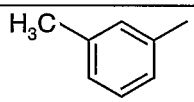
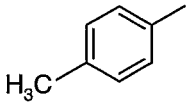
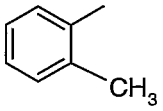
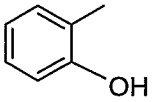
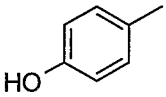
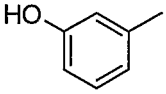
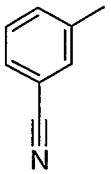
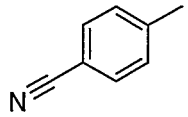
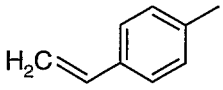
Examples 861-921

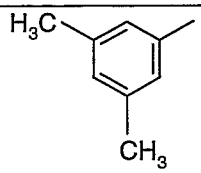
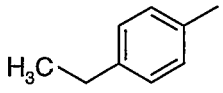
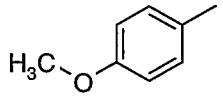
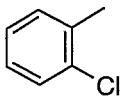
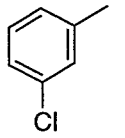
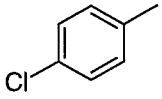
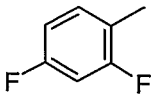
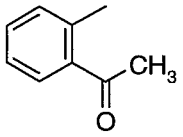
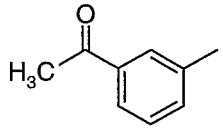
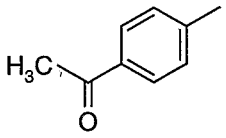
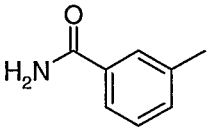
1-(4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

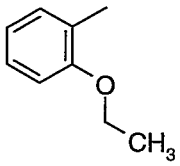
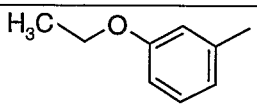
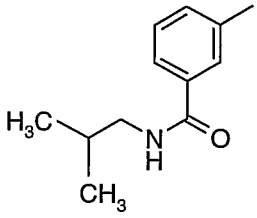
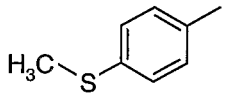
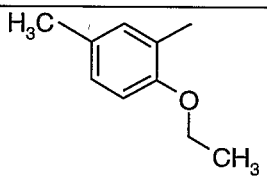
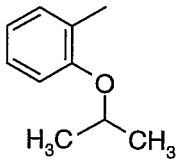
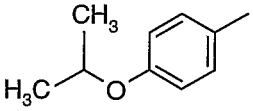
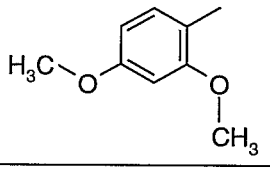
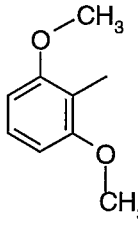
Examples 861-921

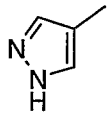
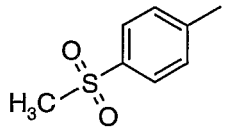
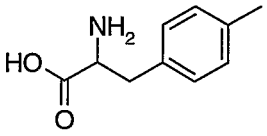
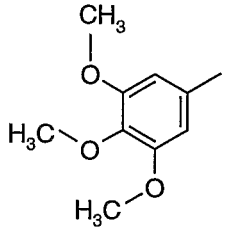
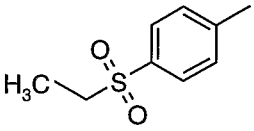
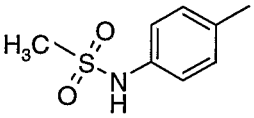
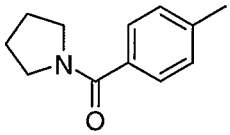
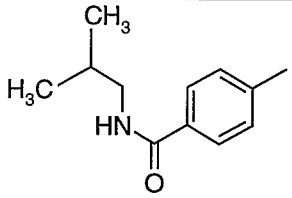
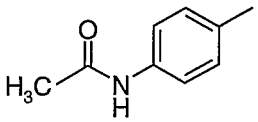
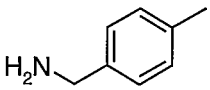


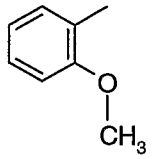
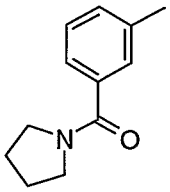
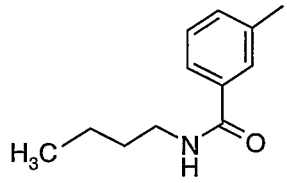
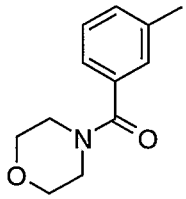
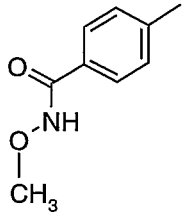
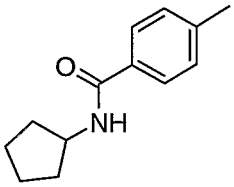
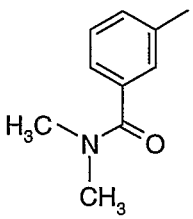
Example	R	Measured Mass (M+H)
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862		391.2139

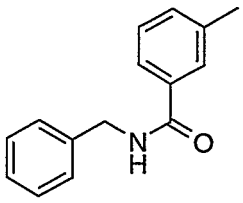
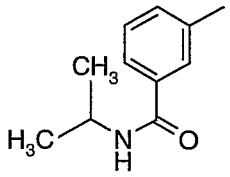
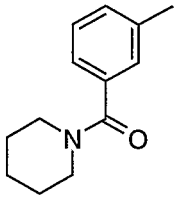
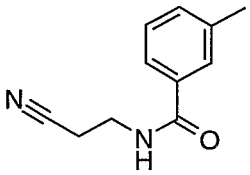
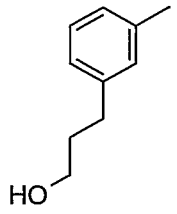
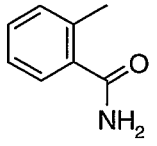
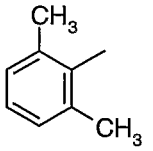
863		392.2069
864		392.2050
865		397.1667
866		397.1695
867		405.2259
868		405.2269
869		405.2283
870		407.2066
871		407.2051
872		407.2068
873		416.2070
874		416.2066
875		417.2247

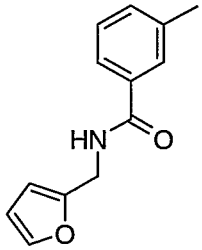
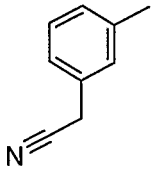
876		419.2472
877		419.2413
878		421.2206
879		425.1762
880		425.1763
881		425.1725
882		427.1958
883		433.2243
884		433.2263
885		433.2231
886		434.2170

887		435.2352
888		435.2393
889		490.2780
890		437.1983
891		449.2522
892		449.2562
893		449.2521
894		451.2303
895		451.2195

896		381.2039
897		469.1895
898		478.2435
899		481.2317
900		483.2026
901		484.2015
902		488.2650
903		490.2784
904		448.2361
905		420.2409

906		421.2241
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912		462.2493

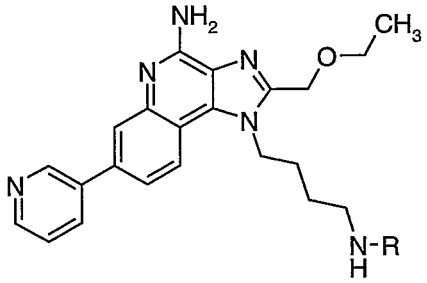
913		524.2609
914		476.2669
915		502.2786
916		487.2453
917		449.2572
918		434.2215
919		419.2444

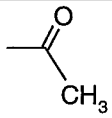
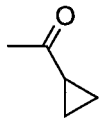
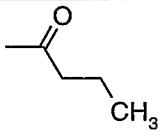
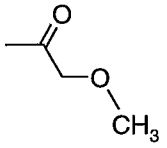
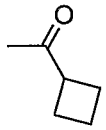
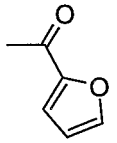
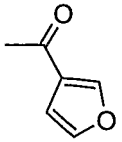
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921		430.2249

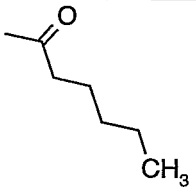
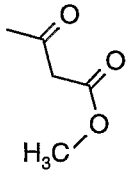
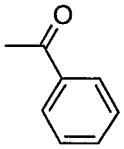
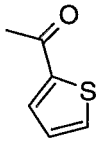
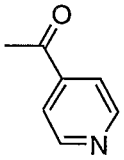
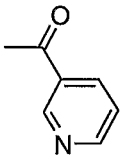
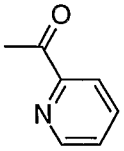
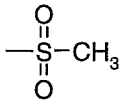
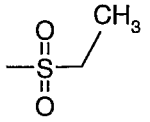
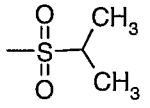
Example 922-955

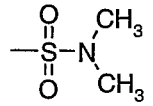
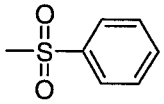
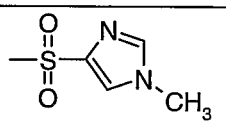
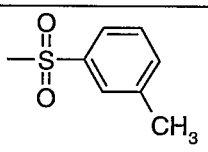
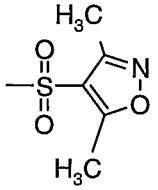
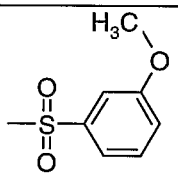
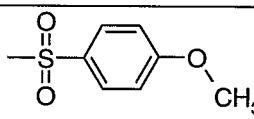
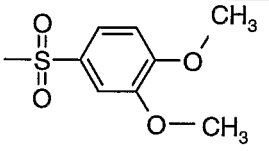
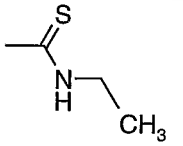
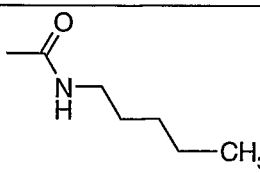
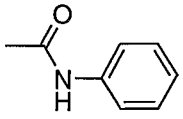
A reagent from the table below, (0.11 mmol, 1.1 equivalents) was added to a test tube containing a solution of 1-(4-aminobutyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (39 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.024 mL, 0.14 mmol, 1.4 equivalents) in chloroform (2 mL). The test tube was capped and placed on a shaker at ambient temperature overnight. One drop of deionized water was then added to each test tube, and the solvent was removed by vacuum centrifugation. The products were purified by prep HPLC according to the methods described above. 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.

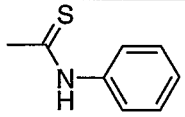
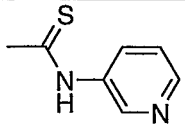
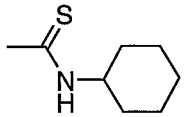
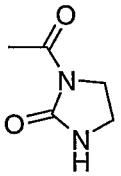
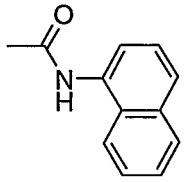
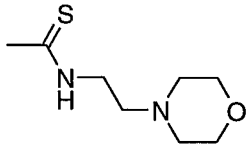
Examples 922-955



Example	Reagent	R	Measured Mass (M+H)
922	Acetyl chloride		433.2328
923	Cyclopropanecarbonyl chloride		459.2498
924	Butyryl chloride		461.2625
925	Methoxyacetyl chloride		463.2431
926	Cyclobutanecarbonyl chloride		473.2641
927	2-Furoyl chloride		485.2261
928	3-Furoyl chloride		485.2284

929	Hexanoyl chloride		489.2979
930	Methyl malonyl chloride		491.2390
931	Benzoyl chloride		495.2462
932	Thiophene-2-carbonyl chloride		501.2066
933	Isonicotinoyl chloride hydrochloride		496.2431
934	Nicotinoyl chloride hydrochloride		496.2466
935	Picolinoyl chloride hydrochloride		496.2476
936	Methanesulfonyl chloride		469.2018
937	Ethanesulfonyl chloride		483.2137
938	Isopropylsulfonyl chloride		497.2370

939	Dimethylsulfamoyl chloride		498.2243
940	Benzenesulfonyl chloride		531.2141
941	1-Methylimidazole-4-sulfonyl chloride		535.2206
942	3-Methylbenzenesulfonyl chloride		545.2297
943	3,5-Dimethylisooxazole-4-sulfonyl chloride		550.2181
944	3-Methoxybenzenesulfonyl chloride		561.2244
945	4-Methoxybenzenesulfonyl chloride		561.2260
946	3,4-Dimethoxybenzenesulfonyl chloride		591.2353
947	Ethyl isothiocyanate		478.2372
948	Pentyl isocyanate		504.3038
949	Phenyl isocyanate		510.2595

950	Phenyl isothiocyanate		526.2362
951	3-Pyridyl isothiocyanate		527.2310
952	Cyclohexyl isothiocyanate		532.2814
953	2-Oxo-1-imidazolidinecarbonyl chloride		503.2503
954	1-Naphthyl isocyanate		560.2722
955	2-Morpholinoethyl isothiocyanate		563.2881

Examples 956-981

Part A

1-(4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (2.62 g, 6.67 mmol) and 3-(*N*-*tert*-butoxycarbonylaminomethyl)phenylboronic acid (2.0 g, 8.0 mmol) were coupled according to the procedure described in Part J of Example 1. Palladium (II) acetate was added as a 5 mg/mL solution in toluene. The reaction was heated for four hours, and the work-up procedure described in Examples 125-135 was followed. The crude product was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 80:20) to provide 2.94 g of *tert*-butyl {3-[4-amino-2-

ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]benzyl}carbamate as a white solid.

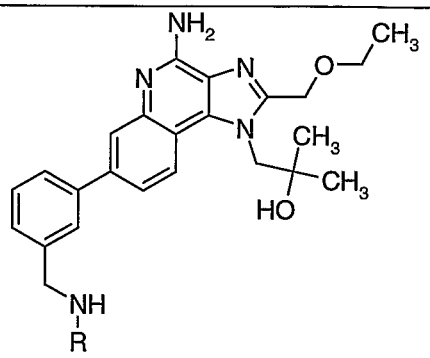
Part B

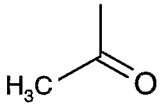
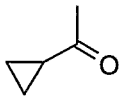
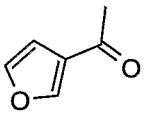
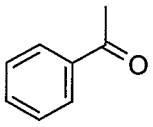
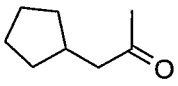
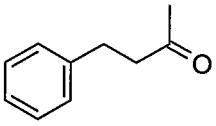
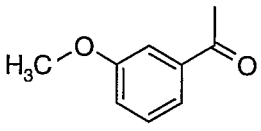
Hydrogen chloride (30 mL of a 3 M solution in ethanol) was added to the material from Part A, and the reaction was heated at reflux for 30 minutes. A precipitate formed. Diethyl ether was added, and the precipitate was isolated by filtration, washed with diethyl ether, and air-dried to provide an off-white solid. The solid was partitioned between 2 M aqueous sodium carbonate, brine, and chloroform. The aqueous layer was extracted with chloroform. The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by HPFC (eluting with chloroform:CMA in a gradient from 100:0 to 50:50). The resulting white solid was recrystallized from acetonitrile, isolated by filtration, washed with cold acetonitrile, and air-dried to provide 1.7 g of 1-[4-amino-7-(3-aminomethylphenyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white solid.

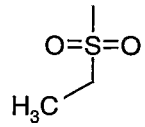
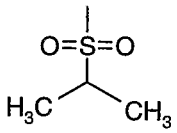
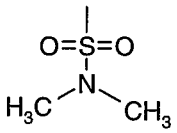
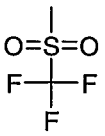
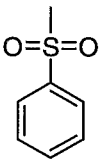
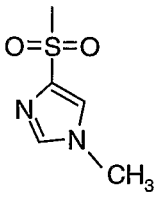
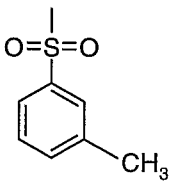
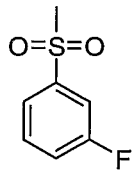
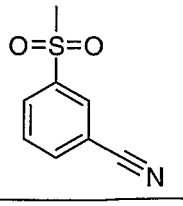
Part C

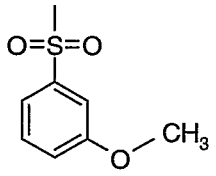
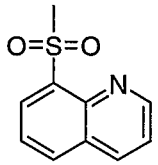
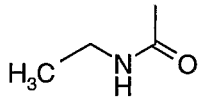
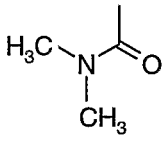
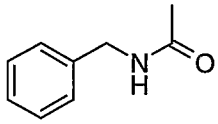
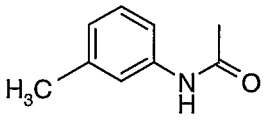
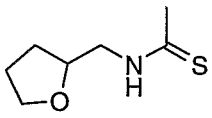
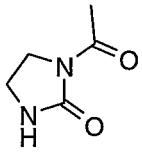
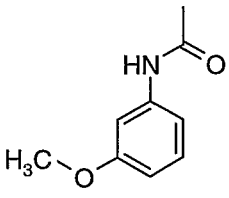
A reagent from the table below, (0.11 mmol, 1.1 equivalents) was added to a test tube containing a solution of 1-[4-amino-7-(3-aminomethylphenyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (40 mg, 0.097 mmol) and *N,N*-diisopropylethylamine (0.022 mL, 0.12 mmol, 1.25 equivalents) in chloroform (2 mL). The test tube was capped and placed on a shaker at ambient temperature overnight. The solvent was removed by vacuum centrifugation. The products were purified by prep HPLC according to the methods described above. 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.

Examples 956-981



Example	Reagent	R	Measured Mass (M+H)
956	None		420.2386
957	Acetyl chloride		462.2499
958	Cyclopropanecarbonyl chloride		488.2661
959	3-Furoyl chloride		514.2431
960	Benzoyl chloride		524.2619
961	Cyclopentylacetyl chloride		530.3090
962	Hydrocinnamoyl chloride		552.2921
963	3-Methoxybenzoyl chloride		554.2740

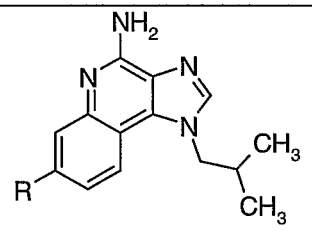
964	Ethanesulfonyl chloride		512.2318
965	Isopropylsulfonyl chloride		526.2449
966	Dimethylsulfamoyl chloride		527.2409
967	Trifluoromethanesulfonyl chloride		552.1876
968	Benzenesulfonyl chloride		560.2306
969	1-Methylimidazole-4-sulfonyl chloride		564.2360
970	3-Methylbenzenesulfonyl chloride		574.2455
971	3-Fluorobenzenesulfonyl chloride		578.2197
972	3-Cyanobenzenesulfonyl chloride		585.2266

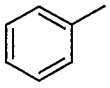
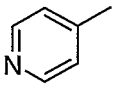
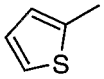
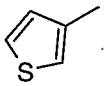
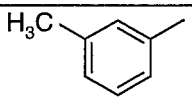
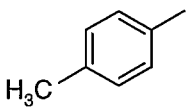
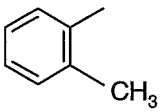
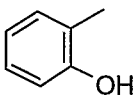
973	3-Methoxybenzenesulfonyl chloride		590.2421
974	8-Quinolinesulfonyl chloride		611.2408
975	Ethyl isocyanate		491.2751
976	*N*,*N*-Dimethylcarbamoyl chloride		491.2740
977	Benzyl isocyanate		553.2889
978	*m*-Tolyl isocyanate		553.2903
979	2-Tetrahydrofurfuryl isothiocyanate		563.2772
980	2-Oxo-1-imidazolidinecarbonyl chloride		532.2656
981	3-Methoxyphenyl isocyanate		569.2869

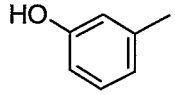
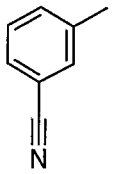
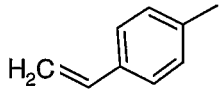
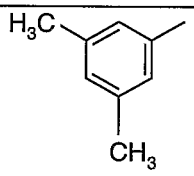
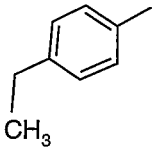
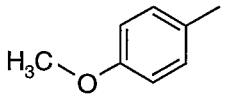
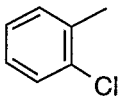
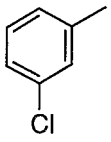
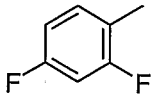
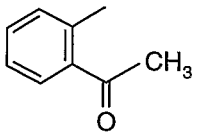
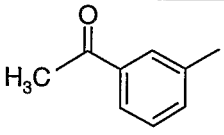
Examples 982-1020

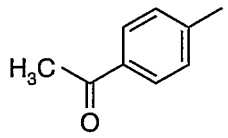
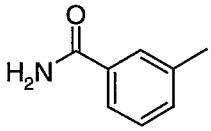
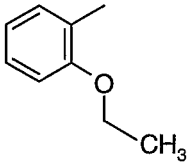
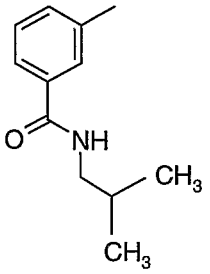
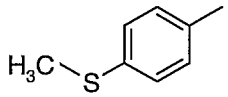
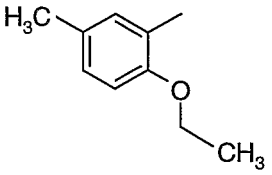
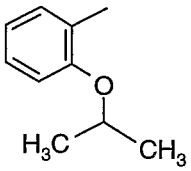
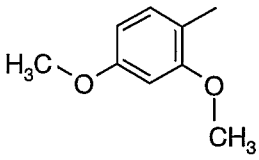
7-Bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine was coupled with the appropriate boronic acid or boronic acid ester according to the procedure described in Examples 20-65. The products were purified by prep HPLC according to the methods described above. The table below shows the structure of the compound obtained in each example and the observed accurate mass for the isolated trifluoroacetate salt.

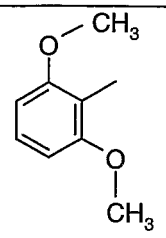
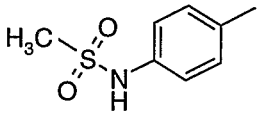
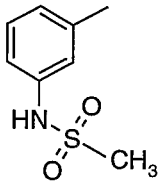
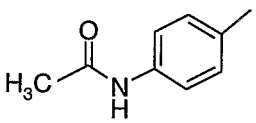
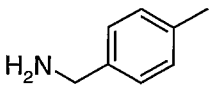
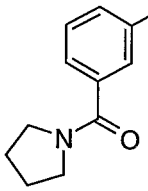
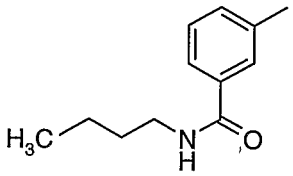
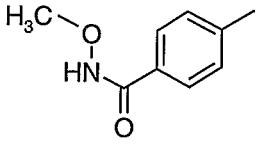
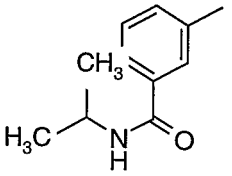
Examples 982-1020

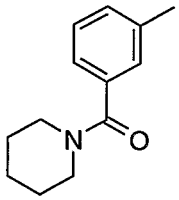
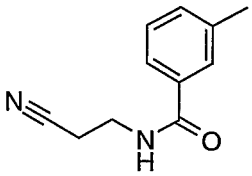
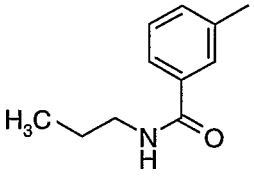


Example	R	Measured Mass (M+H)
982		317.1781
983		318.1737
984		323.1358
985		323.1355
986		331.1947
987		331.1948
988		331.1940
989		333.1740

990		333.1720
991		342.1749
992		343.1926
993		345.2101
994		345.2080
995		347.1886
996		351.1398
997		351.1399
998		353.1572
999		359.1885
1000		359.1897

1001		359.1907
1002		360.1859
1003		361.2050
1004		416.2472
1005		363.1660
1006		375.2195
1007		375.2171
1008		377.2009

1009		377.2013
1010		410.1660
1011		410.1689
1012		374.2006
1013		346.2040
1014		414.2326
1015		416.2472
1016		390.1950
1017		402.2324

1018		428.2479
1019		413.2098
1020		402.2303

CYTOKINE INDUCTION IN HUMAN CELLS

Many compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α when tested using the method described below. Particular examples include but are not limited to the compounds of Examples 1-10, 12, 16, 18-21, 24-31, 43, 44, 51, 54, 55, 63, 66-101, 103-117, 119, 121-203, 205-390, 392-400, 403-407, 409-412, 414-418, 420, 425, 426, 428, 430-440, 442-446, 464-466, 468, 472-474, 476, 493, 494, 508-663, 807-830, 832-837, 839-841, 843, 844, 847-849, 852, 856, 858, 860-916, and 922-955.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, 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 EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) 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.

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 (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 with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for

interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

TNF-α INHIBITION IN MOUSE CELLS

Certain compounds of the invention have been found to modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below. Particular examples include but are not limited to the compounds of Examples 14, 15, and 481.

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

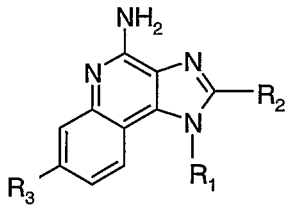
A solution of test compound (200 μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The 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.

Exemplary Compounds

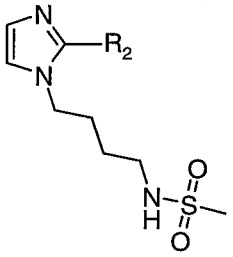
Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (XLV) wherein R_1, R_2, and R_3 are defined immediately below.



XLV

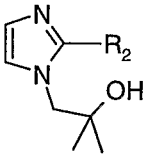
R_1 substituents:

4-methanesulfonylaminobutyl (as shown with only a portion of the ring system)



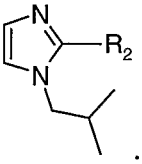
;

2-hydroxy-2-methylpropyl (as shown with only a portion of the ring system)



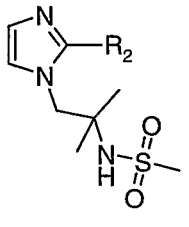
;

2-methylpropyl (as shown with only a portion of the ring system)

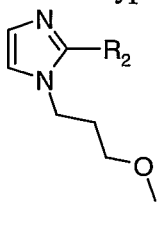


;

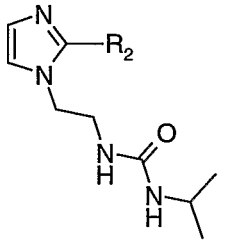
2-methanesulfonylamino-2-methylpropyl (as shown with only a portion of the ring system)


;

3-methoxypropyl (as shown with only a portion of the ring system)

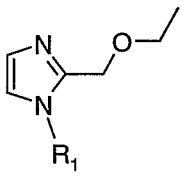

; and

2-[3-(1-methylethyl)ureido]ethyl (as shown with only a portion of the ring system)

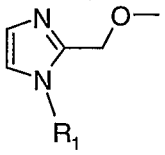

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R_2 substituents:

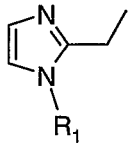
ethoxymethyl (as shown with only a portion of the ring system)


;

methoxymethyl (as shown with only a portion of the ring system)

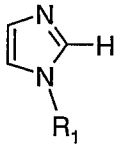

;

ethyl (as shown with only a portion of the ring system)



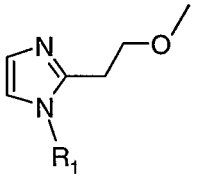
;

hydrogen (as shown with only a portion of the ring system)



; and

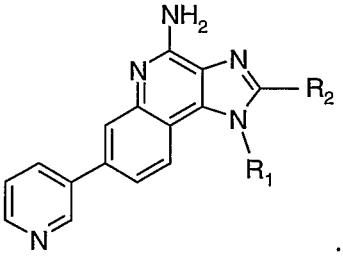
2-methoxyethyl (as shown with only a portion of the ring system)



.

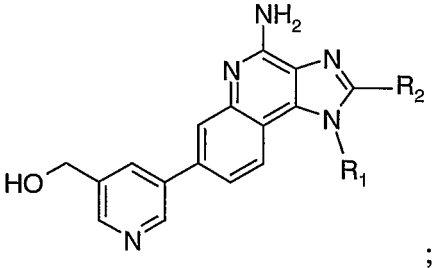
R_3 substituents:

pyridin-3-yl (as shown attached to the ring system)



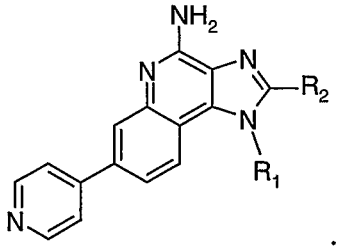
;

5-hydroxymethylpyridin-3-yl (as shown attached to the ring system)



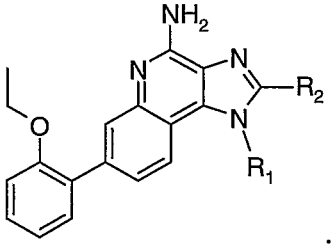
;

pyridin-4-yl (as shown attached to the ring system)



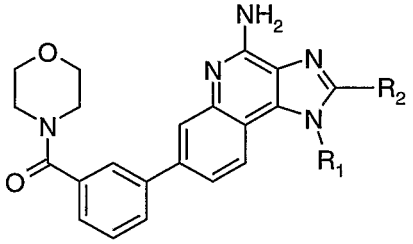
;

2-ethoxyphenyl (as shown attached to the ring system)



; and

3-(morpholine-4-carbonyl)phenyl (as shown attached to the ring system)



.

Certain exemplary compounds have the above Formula (XLV) and the following substituents, wherein each line of the table represents a specific compound.

R_1	R_2	R_3
4-methanesulfonylaminobutyl	ethoxymethyl	pyridin-3-yl
4-methanesulfonylaminobutyl	ethoxymethyl	5-hydroxymethylpyridin-3-yl
4-methanesulfonylaminobutyl	ethoxymethyl	pyridin-4-yl
4-methanesulfonylaminobutyl	ethoxymethyl	2-ethoxyphenyl
4-methanesulfonylaminobutyl	ethoxymethyl	3-(morpholine-4-carbonyl)phenyl
4-methanesulfonylaminobutyl	methoxymethyl	pyridin-3-yl
4-methanesulfonylaminobutyl	methoxymethyl	5-hydroxymethylpyridin-3-yl
4-methanesulfonylaminobutyl	methoxymethyl	pyridin-4-yl

4-methanesulfonylaminobutyl	methoxymethyl	2-ethoxyphenyl
4-methanesulfonylaminobutyl	methoxymethyl	3-(morpholine-4-carbonyl)phenyl
4-methanesulfonylaminobutyl	ethyl	pyridin-3-yl
4-methanesulfonylaminobutyl	ethyl	5-hydroxymethylpyridin-3-yl
4-methanesulfonylaminobutyl	ethyl	pyridin-4-yl
4-methanesulfonylaminobutyl	ethyl	2-ethoxyphenyl
4-methanesulfonylaminobutyl	ethyl	3-(morpholine-4-carbonyl)phenyl
4-methanesulfonylaminobutyl	hydrogen	pyridin-3-yl
4-methanesulfonylaminobutyl	hydrogen	5-hydroxymethylpyridin-3-yl
4-methanesulfonylaminobutyl	hydrogen	pyridin-4-yl
4-methanesulfonylaminobutyl	hydrogen	2-ethoxyphenyl
4-methanesulfonylaminobutyl	hydrogen	3-(morpholine-4-carbonyl)phenyl
4-methanesulfonylaminobutyl	2-methoxyethyl	pyridin-3-yl
4-methanesulfonylaminobutyl	2-methoxyethyl	5-hydroxymethylpyridin-3-yl
4-methanesulfonylaminobutyl	2-methoxyethyl	pyridin-4-yl
4-methanesulfonylaminobutyl	2-methoxyethyl	2-ethoxyphenyl
4-methanesulfonylaminobutyl	2-methoxyethyl	3-(morpholine-4-carbonyl)phenyl
2-hydroxy-2-methylpropyl	ethoxymethyl	pyridin-3-yl
2-hydroxy-2-methylpropyl	ethoxymethyl	5-hydroxymethylpyridin-3-yl
2-hydroxy-2-methylpropyl	ethoxymethyl	pyridin-4-yl
2-hydroxy-2-methylpropyl	ethoxymethyl	2-ethoxyphenyl
2-hydroxy-2-methylpropyl	ethoxymethyl	3-(morpholine-4-carbonyl)phenyl
2-hydroxy-2-methylpropyl	methoxymethyl	pyridin-3-yl
2-hydroxy-2-methylpropyl	methoxymethyl	5-hydroxymethylpyridin-3-yl
2-hydroxy-2-methylpropyl	methoxymethyl	pyridin-4-yl
2-hydroxy-2-methylpropyl	methoxymethyl	2-ethoxyphenyl
2-hydroxy-2-methylpropyl	methoxymethyl	3-(morpholine-4-carbonyl)phenyl
2-hydroxy-2-methylpropyl	ethyl	pyridin-3-yl
2-hydroxy-2-methylpropyl	ethyl	5-hydroxymethylpyridin-3-yl
2-hydroxy-2-methylpropyl	ethyl	pyridin-4-yl
2-hydroxy-2-methylpropyl	ethyl	2-ethoxyphenyl
2-hydroxy-2-methylpropyl	ethyl	3-(morpholine-4-carbonyl)phenyl
2-hydroxy-2-methylpropyl	hydrogen	pyridin-3-yl
2-hydroxy-2-methylpropyl	hydrogen	5-hydroxymethylpyridin-3-

		yl
2-hydroxy-2-methylpropyl	hydrogen	pyridin-4-yl
2-hydroxy-2-methylpropyl	hydrogen	2-ethoxyphenyl
2-hydroxy-2-methylpropyl	hydrogen	3-(morpholine-4-carbonyl)phenyl
2-hydroxy-2-methylpropyl	2-methoxyethyl	pyridin-3-yl
2-hydroxy-2-methylpropyl	2-methoxyethyl	5-hydroxymethylpyridin-3-yl
2-hydroxy-2-methylpropyl	2-methoxyethyl	pyridin-4-yl
2-hydroxy-2-methylpropyl	2-methoxyethyl	2-ethoxyphenyl
2-hydroxy-2-methylpropyl	2-methoxyethyl	3-(morpholine-4-carbonyl)phenyl
2-methylpropyl	ethoxymethyl	pyridin-3-yl
2-methylpropyl	ethoxymethyl	5-hydroxymethylpyridin-3-yl
2-methylpropyl	ethoxymethyl	pyridin-4-yl
2-methylpropyl	ethoxymethyl	2-ethoxyphenyl
2-methylpropyl	ethoxymethyl	3-(morpholine-4-carbonyl)phenyl
2-methylpropyl	methoxymethyl	pyridin-3-yl
2-methylpropyl	methoxymethyl	5-hydroxymethylpyridin-3-yl
2-methylpropyl	methoxymethyl	pyridin-4-yl
2-methylpropyl	methoxymethyl	2-ethoxyphenyl
2-methylpropyl	methoxymethyl	3-(morpholine-4-carbonyl)phenyl
2-methylpropyl	ethyl	pyridin-3-yl
2-methylpropyl	ethyl	5-hydroxymethylpyridin-3-yl
2-methylpropyl	ethyl	pyridin-4-yl
2-methylpropyl	ethyl	2-ethoxyphenyl
2-methylpropyl	ethyl	3-(morpholine-4-carbonyl)phenyl
2-methylpropyl	hydrogen	pyridin-3-yl
2-methylpropyl	hydrogen	5-hydroxymethylpyridin-3-yl
2-methylpropyl	hydrogen	pyridin-4-yl
2-methylpropyl	hydrogen	2-ethoxyphenyl
2-methylpropyl	hydrogen	3-(morpholine-4-carbonyl)phenyl
2-methylpropyl	2-methoxyethyl	pyridin-3-yl
2-methylpropyl	2-methoxyethyl	5-hydroxymethylpyridin-3-yl
2-methylpropyl	2-methoxyethyl	pyridin-4-yl
2-methylpropyl	2-methoxyethyl	2-ethoxyphenyl
2-methylpropyl	2-methoxyethyl	3-(morpholine-4-carbonyl)phenyl

2-methanesulfonylamino-2-methylpropyl	ethoxymethyl	pyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	ethoxymethyl	5-hydroxymethylpyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	ethoxymethyl	pyridin-4-yl
2-methanesulfonylamino-2-methylpropyl	ethoxymethyl	2-ethoxyphenyl
2-methanesulfonylamino-2-methylpropyl	ethoxymethyl	3-(morpholine-4-carbonyl)phenyl
2-methanesulfonylamino-2-methylpropyl	methoxymethyl	pyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	methoxymethyl	5-hydroxymethylpyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	methoxymethyl	pyridin-4-yl
2-methanesulfonylamino-2-methylpropyl	methoxymethyl	2-ethoxyphenyl
2-methanesulfonylamino-2-methylpropyl	methoxymethyl	3-(morpholine-4-carbonyl)phenyl
2-methanesulfonylamino-2-methylpropyl	ethyl	pyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	ethyl	5-hydroxymethylpyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	ethyl	pyridin-4-yl
2-methanesulfonylamino-2-methylpropyl	ethyl	2-ethoxyphenyl
2-methanesulfonylamino-2-methylpropyl	ethyl	3-(morpholine-4-carbonyl)phenyl
2-methanesulfonylamino-2-methylpropyl	hydrogen	pyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	hydrogen	5-hydroxymethylpyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	hydrogen	pyridin-4-yl
2-methanesulfonylamino-2-methylpropyl	hydrogen	2-ethoxyphenyl
2-methanesulfonylamino-2-methylpropyl	hydrogen	3-(morpholine-4-carbonyl)phenyl
2-methanesulfonylamino-2-methylpropyl	2-methoxyethyl	pyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	2-methoxyethyl	5-hydroxymethylpyridin-3-yl
2-methanesulfonylamino-2-methylpropyl	2-methoxyethyl	pyridin-4-yl
2-methanesulfonylamino-2-	2-methoxyethyl	2-ethoxyphenyl

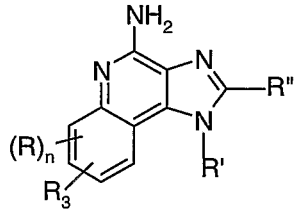
methylpropyl		
2-methanesulfonylamino-2-methylpropyl	2-methoxyethyl	3-(morpholine-4-carbonyl)phenyl
3-methoxypropyl	ethoxymethyl	pyridin-3-yl
3-methoxypropyl	ethoxymethyl	5-hydroxymethylpyridin-3-yl
3-methoxypropyl	ethoxymethyl	pyridin-4-yl
3-methoxypropyl	ethoxymethyl	2-ethoxyphenyl
3-methoxypropyl	ethoxymethyl	3-(morpholine-4-carbonyl)phenyl
3-methoxypropyl	methoxymethyl	pyridin-3-yl
3-methoxypropyl	methoxymethyl	5-hydroxymethylpyridin-3-yl
3-methoxypropyl	methoxymethyl	pyridin-4-yl
3-methoxypropyl	methoxymethyl	2-ethoxyphenyl
3-methoxypropyl	methoxymethyl	3-(morpholine-4-carbonyl)phenyl
3-methoxypropyl	ethyl	pyridin-3-yl
3-methoxypropyl	ethyl	5-hydroxymethylpyridin-3-yl
3-methoxypropyl	ethyl	pyridin-4-yl
3-methoxypropyl	ethyl	2-ethoxyphenyl
3-methoxypropyl	ethyl	3-(morpholine-4-carbonyl)phenyl
3-methoxypropyl	hydrogen	pyridin-3-yl
3-methoxypropyl	hydrogen	5-hydroxymethylpyridin-3-yl
3-methoxypropyl	hydrogen	pyridin-4-yl
3-methoxypropyl	hydrogen	2-ethoxyphenyl
3-methoxypropyl	hydrogen	3-(morpholine-4-carbonyl)phenyl
3-methoxypropyl	2-methoxyethyl	pyridin-3-yl
3-methoxypropyl	2-methoxyethyl	5-hydroxymethylpyridin-3-yl
3-methoxypropyl	2-methoxyethyl	pyridin-4-yl
3-methoxypropyl	2-methoxyethyl	2-ethoxyphenyl
3-methoxypropyl	2-methoxyethyl	3-(morpholine-4-carbonyl)phenyl
2-[3-(1-methylethyl)ureido]ethyl	ethoxymethyl	pyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	ethoxymethyl	5-hydroxymethylpyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	ethoxymethyl	pyridin-4-yl
2-[3-(1-methylethyl)ureido]ethyl	ethoxymethyl	2-ethoxyphenyl
2-[3-(1-	ethoxymethyl	3-(morpholine-4-

methylethyl)ureido]ethyl		carbonyl)phenyl
2-[3-(1-methylethyl)ureido]ethyl	methoxymethyl	pyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	methoxymethyl	5-hydroxymethylpyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	methoxymethyl	pyridin-4-yl
2-[3-(1-methylethyl)ureido]ethyl	methoxymethyl	2-ethoxyphenyl
2-[3-(1-methylethyl)ureido]ethyl	methoxymethyl	3-(morpholine-4-carbonyl)phenyl
2-[3-(1-methylethyl)ureido]ethyl	ethyl	pyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	ethyl	5-hydroxymethylpyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	ethyl	pyridin-4-yl
2-[3-(1-methylethyl)ureido]ethyl	ethyl	2-ethoxyphenyl
2-[3-(1-methylethyl)ureido]ethyl	ethyl	3-(morpholine-4-carbonyl)phenyl
2-[3-(1-methylethyl)ureido]ethyl	hydrogen	pyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	hydrogen	5-hydroxymethylpyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	hydrogen	pyridin-4-yl
2-[3-(1-methylethyl)ureido]ethyl	hydrogen	2-ethoxyphenyl
2-[3-(1-methylethyl)ureido]ethyl	hydrogen	3-(morpholine-4-carbonyl)phenyl
2-[3-(1-methylethyl)ureido]ethyl	2-methoxyethyl	pyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	2-methoxyethyl	5-hydroxymethylpyridin-3-yl
2-[3-(1-methylethyl)ureido]ethyl	2-methoxyethyl	pyridin-4-yl
2-[3-(1-methylethyl)ureido]ethyl	2-methoxyethyl	2-ethoxyphenyl
2-[3-(1-methylethyl)ureido]ethyl	2-methoxyethyl	3-(morpholine-4-carbonyl)phenyl

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 formula (I):



I

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R' and R" are independently selected from the group consisting of hydrogen and non-interfering substitutents;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroarylox, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

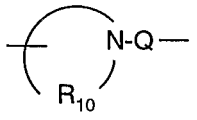
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

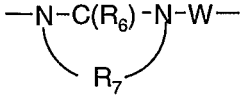
$-C(R_6)-N(R_8)-$,

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

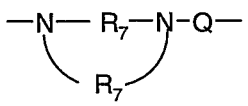
$-C(R_6)-N(OR_9)-$,

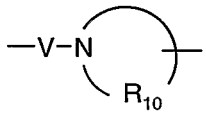


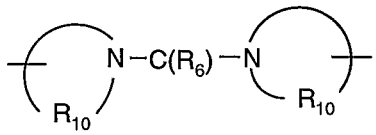
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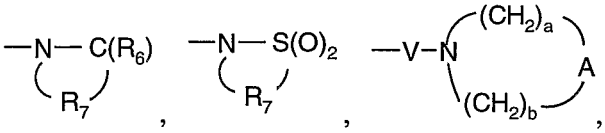

, and

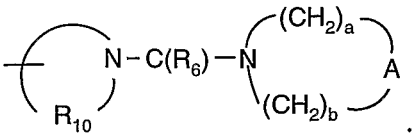

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

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

R_5 is selected from the group consisting of:


,


and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, 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 $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein the compound or salt induces the biosynthesis of one or more cytokines.

3. The compound or salt of claim 1 wherein the compound or salt inhibits the biosynthesis of TNF.

4. The compound or salt of claim 1 wherein -Z- is a bond.

5. The compound or salt of claim 1 wherein R_3 is -Z-Ar.

6. The compound or salt of claim 1 wherein R_3 is $-Z-Ar'-Y-R_4$ or $-Z-Ar'-X-Y-R_4$.

7. The compound or salt of claim 1 wherein n is 0.

8. The compound or salt of claim 1 wherein R' is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

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

$-X-R_5$;

wherein each X is independently selected, each Y is independently selected, each R_4 is independently selected, and each R_5 is independently selected.

9. The compound or salt of claim 1 wherein R" is selected from the group consisting of:

$-R_4$,

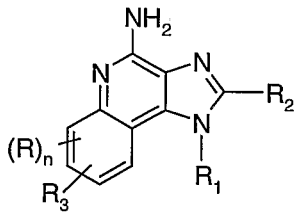
$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

wherein each X is independently selected, each Y is independently selected, each R_4 is independently selected, and each R_5 is independently selected.

10. A compound of formula (II):



II

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

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

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$,

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

$-Z-Ar'-R_5$, and

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

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy,

haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

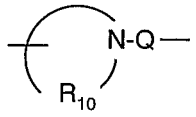
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

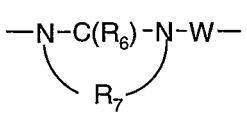
$-C(R_6)-N(R_8)-$,

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

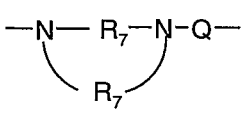
$-C(R_6)-N(OR_9)-$,



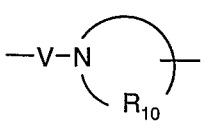
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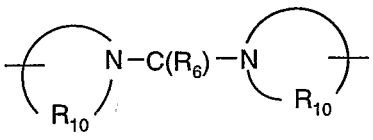
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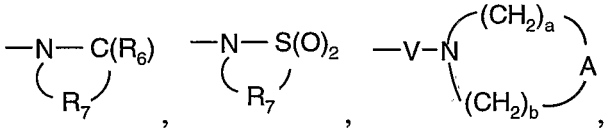


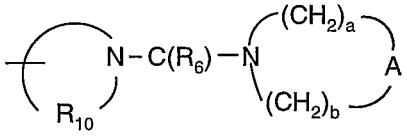
;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:



and 

;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_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.

11. The compound or salt of claim 10 wherein the compound or salt induces the biosynthesis of one or more cytokines.

12. The compound or salt of claim 10 wherein the compound or salt inhibits the biosynthesis of TNF.

13. The compound or salt of claim 10 wherein -Z- is a bond.

14. The compound or salt of claim 10 wherein n is 0.

15. The compound or salt of claim 10 wherein R_3 is -Z-Ar.

16. The compound or salt of claim 10 wherein R_3 is selected from the group consisting of phenyl, pyridyl, pyrrolyl, thienyl, and furyl; each of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, carboxy, and cyano.

17. The compound or salt of claim 10 wherein R_3 is -Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4, or -Z-Ar'-R_5.

18. The compound or salt of claim 17 wherein Ar' is phenyl or pyridyl;

Y is selected from the group consisting of:

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

-C(O)-,

-$N(R_8)$-Q-,

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

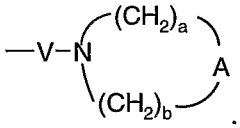
-$C(R_6)$-$N(OR_9)$-;

wherein Q is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-; and R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and alkoxyalkylenyl;

X is C_{1-4} alkylene;

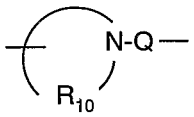
R_4 is selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl; and

R_5 is

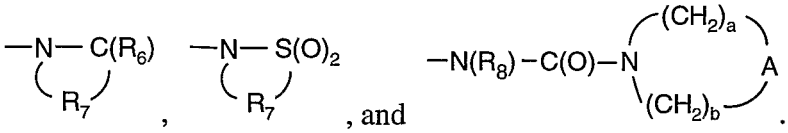


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19. The compound or salt of claim 10 wherein R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X-Y-R_4, and -X-R_5; wherein X is alkylene; Y is selected from the group consisting of -$N(R_8)$-C(O)-, -$N(R_8)$-$S(O)_2$-, -$N(R_8)$-C(O)-$N(R_8)$-, and



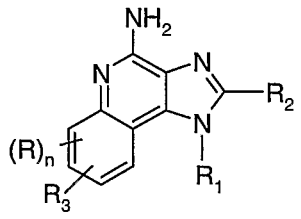
; R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl; and R_5 is selected from the group consisting of



, , and .

20. The compound or salt of claim 10 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

21. A compound of formula (IIa):



IIa

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

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

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar and

$-Z-Ar'-Y-R_4$;

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

each Y is independently selected from the group consisting of:

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

$-CR_6-$,

$-CR_6-O-$,

$-O-CR_6-$,

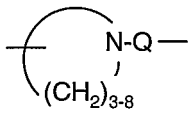
$-O-C(O)-O-$,

$-NR_8-Q-$,

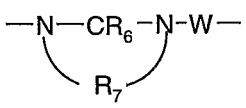
$-CR_6-NR_8-$,

$-O-CR_6-NR_8-$,

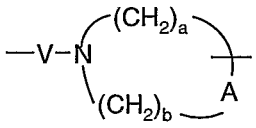
$-CR_6-N(OR_9)-$



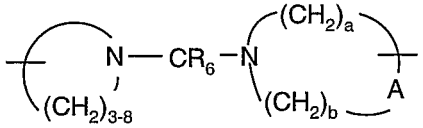
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, and



;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

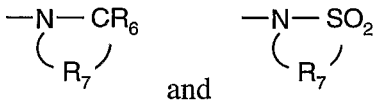
Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently

selected from the group consisting of alkyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently 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;

each R_8 present is independently selected from the group consisting of hydrogen, alkyl, and arylalkyl;

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

A is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-NR_4-$, and $-CH_2-$;

Q is selected from the group consisting of $-CR_6-$, $-SO_2-$, $-CR_6-NR_8-W-$, $-SO_2-NR_8-$, $-CR_6-O-$, and $-CR_6-N(OR_9)-$;

V is selected from the group consisting of $-CR_6-$, $-O-CR_6-$, and $-NR_8-CR_6-$;
W is selected from the group consisting of a bond, -C(O)-, and $-SO_2-$; 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.

22. The compound or salt of claim 21 wherein the compound or salt induces the biosynthesis of one or more cytokines.

23. The compound or salt of claim 21 wherein the compound or salt inhibits the biosynthesis of TNF.

24. The compound or salt of claim 21 wherein R_1 is R_4 or $-X-Y-R_4$.

25. The compound or salt of claim 21 wherein R_1 is alkyl or hydroxyalkyl.

26. The compound or salt of claim 24 wherein -X- is C_{2-6} alkylene.

27. The compound or salt of claim 24 wherein -Y- is $-S(O)_{0-2}-$ or $-NR_8-Q-$.

28. The compound or salt of claim 21 wherein R_2 is R_4.

29. The compound or salt of claim 21 wherein R_2 is alkyl or alkoxyalkyl.

30. The compound or salt of claim 21 wherein R_3 is -Z-Ar.

31. The compound or salt of claim 30 wherein -Z- is a bond.

32. The compound or salt of claim 30 wherein -Ar is unsubstituted aryl or heteroaryl.

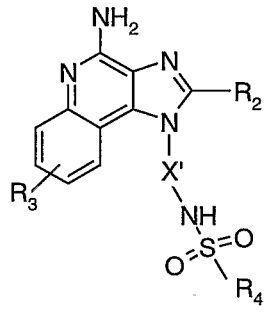
33. The compound or salt of claim 32 wherein -Ar is phenyl, thienyl or pyridyl.

34. The compound or salt of claim 21 wherein R_3 is attached at the 7-position.

35. The compound or salt of claim 21 wherein R_3 is attached at the 8-position.

36. The compound or salt of claim 21 wherein n is 0.

37. A compound of formula (III):



III

wherein:

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

X' is C_{2-8} alkylene;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

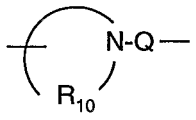
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

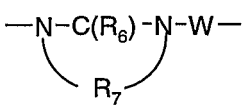
$-C(R_6)-N(R_8)-$,

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

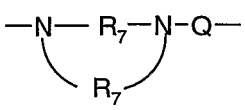
$-C(R_6)-N(OR_9)-$,



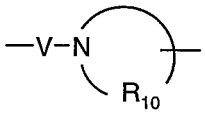
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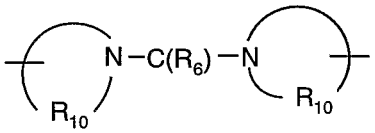
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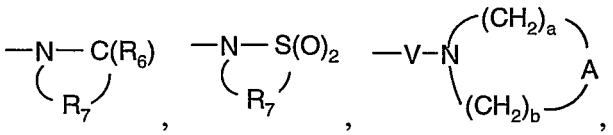


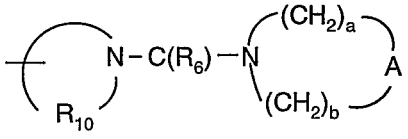
;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:





and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, 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 $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

38. The compound or salt of claim 37 wherein the compound or salt induces the biosynthesis of one or more cytokines.

39. The compound or salt of claim 37 wherein the compound or salt inhibits the biosynthesis of TNF.

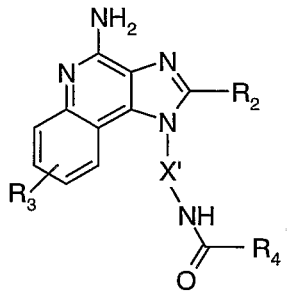
40. The compound or salt of claim 37 wherein X' is $-CH_2-C(CH_3)_2-$.

41. The compound or salt of claim 37 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

42. The compound or salt of claim 37 wherein R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

43. The compound or salt of claim 37 wherein R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

44. A compound of Formula (IV):



IV

wherein:

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

X' is C_{2-8} alkylene;

each Y is independently 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)-,

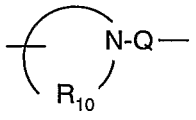
-O-C(O)-O-,

-N(R_8)-Q-,

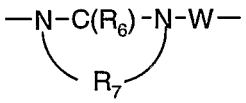
-C(R_6)-N(R_8)-,

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

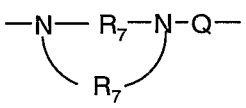
-C(R_6)-N(OR_9)-,



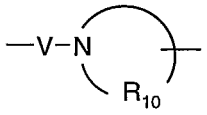
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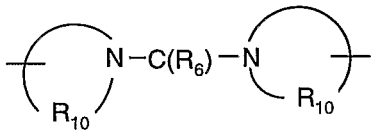
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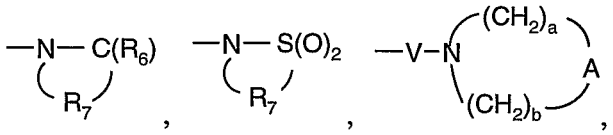
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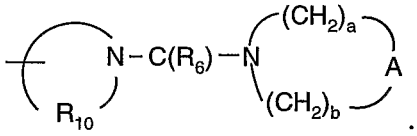
Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:



and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, 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 $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

45. The compound or salt of claim 44 wherein the compound or salt induces the biosynthesis of one or more cytokines.

46. The compound or salt of claim 44 wherein the compound or salt inhibits the biosynthesis of TNF.

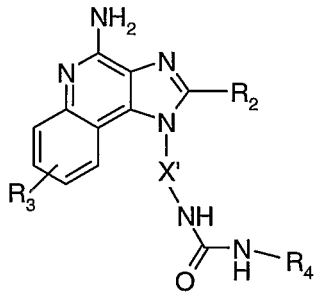
47. The compound or salt of claim 44 wherein X' is $-CH_2-C(CH_3)_2-$.

48. The compound or salt of claim 44 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

49. The compound or salt of claim 44 wherein R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

50. The compound or salt of claim 44 wherein R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

51. A compound of Formula (V):



V

wherein:

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$,

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

$-Z-Ar'-R_5$, and

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

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

X' is C_{2-8} alkylene;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

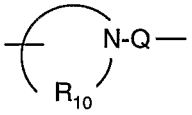
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

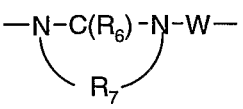
$-C(R_6)-N(R_8)-$,

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

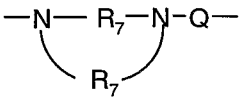
$-C(R_6)-N(OR_9)-$,



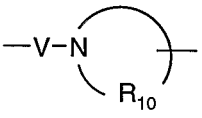
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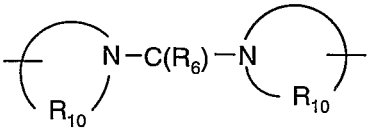
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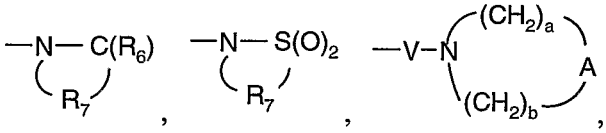
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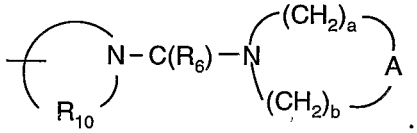
Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:



and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, 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.

52. The compound or salt of claim 51 wherein the compound or salt induces the biosynthesis of one or more cytokines.

53. The compound or salt of claim 51 wherein the compound or salt inhibits the biosynthesis of TNF.

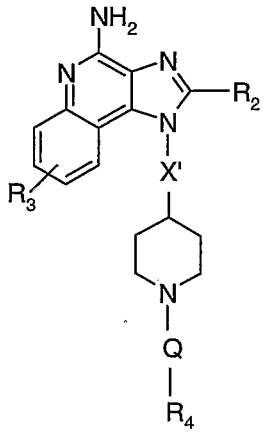
54. The compound or salt of claim 51 wherein X' is $-CH_2-C(CH_3)_2-$.

55. The compound or salt of claim 51 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

56. The compound or salt of claim 51 wherein R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

57. The compound or salt of claim 51 wherein R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

58. A compound of Formula (VI):



VI

wherein:

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$,

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

$-Z-Ar'-R_5$, and

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

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy,

heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

X' is C_{2-8} alkylene;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

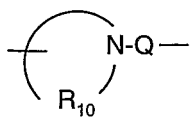
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

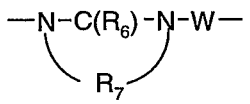
$-C(R_6)-N(R_8)-$,

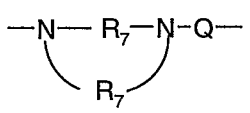
$-O-C(R_6)-N(R_8)-$,

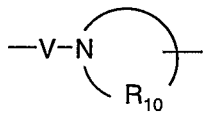
$-C(R_6)-N(OR_9)-$,

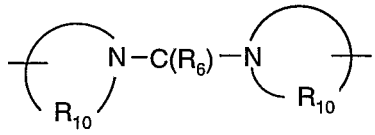


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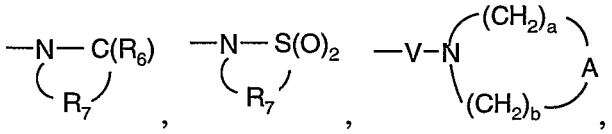
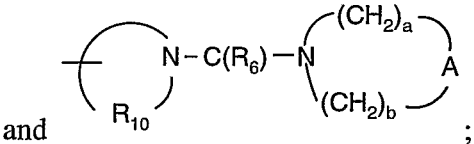

, and


;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:

and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, 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 $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

59. The compound or salt of claim 58 wherein the compound or salt induces the biosynthesis of one or more cytokines.

60. The compound or salt of claim 58 wherein the compound or salt inhibits the biosynthesis of TNF.

61. The compound or salt of claim 58 wherein Q is -C(O)-, $-S(O)_2-$, or

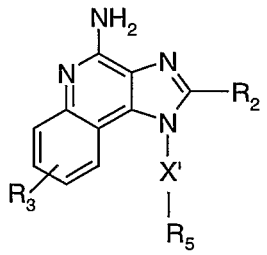
-C(O)-NH-.

62. The compound or salt of claim 58 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

63. The compound or salt of claim 58 wherein R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

64. The compound or salt of claim 58 wherein R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

65. A compound of Formula (VII):



VII

wherein:

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

X' is C_{2-8} alkylene;

each Y is independently 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)-,

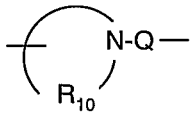
-O-C(O)-O-,

-N(R_8)-Q-,

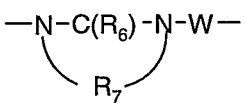
-C(R_6)-N(R_8)-,

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

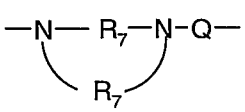
-C(R_6)-N(OR_9)-,



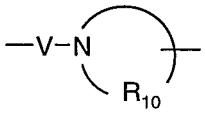
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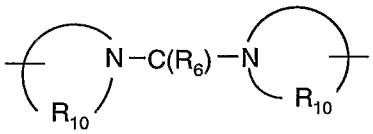
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, and



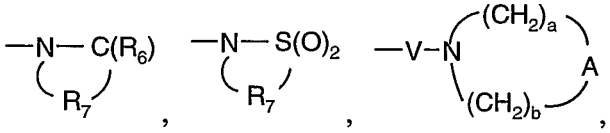
;

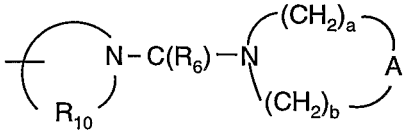
Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:





and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, 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 $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

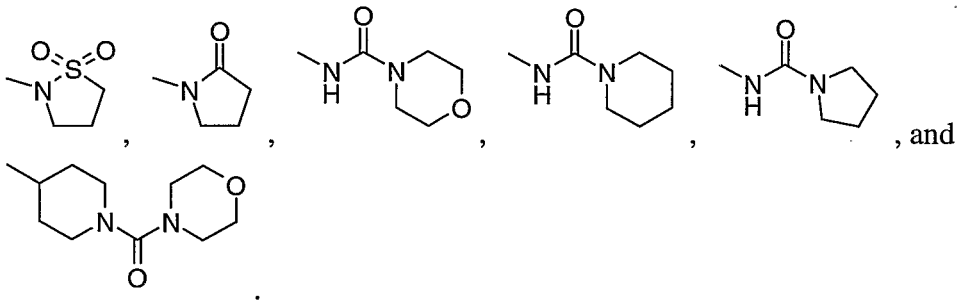
66. The compound or salt of claim 65 wherein the compound or salt induces the biosynthesis of one or more cytokines.

67. The compound or salt of claim 65 wherein the compound or salt inhibits the biosynthesis of TNF.

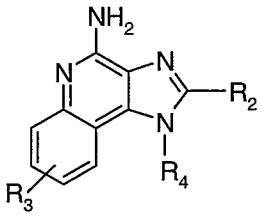
68. The compound or salt of claim 65 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

69. The compound or salt of claim 65 wherein R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

70. The compound or salt of claim 65 wherein each R_5 is independently selected from the group consisting of:


, and

71. A compound of Formula (VIII):



VIII

wherein:

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$,

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

$-Z-Ar'-R_5$, and

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

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

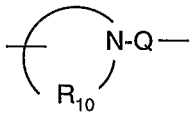
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

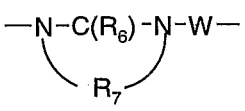
$-C(R_6)-N(R_8)-$,

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

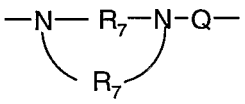
$-C(R_6)-N(OR_9)-$,



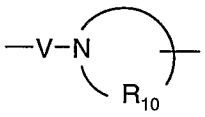
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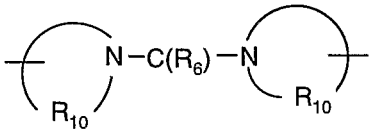
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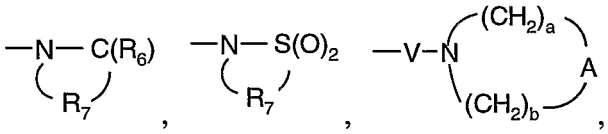
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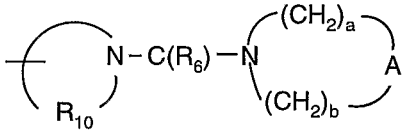
Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:



and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, 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 the compound or salt induces the biosynthesis of one or more cytokines.

73. The compound or salt of claim 71 wherein the compound or salt inhibits the biosynthesis of TNF.

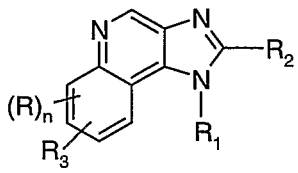
74. The compound or salt of claim 71 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkylenyl.

75. The compound or salt of claim 71 wherein R_3 is phenyl or pyridyl, either of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylcarbonylaminoalkylenyl, and arylcarbonylaminoalkylenyl.

76. The compound or salt of claim 71 wherein R_4 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-4} alkyl-O-C_{1-4} alkylenyl, and aryl-O-C_{1-4} alkylenyl.

77. The compound or salt of claim 76 wherein R_4 is selected from the group consisting of 2-methylpropyl, 2-hydroxy-2-methylpropyl, 3-methoxypropyl, and phenoxyethyl.

78. A compound of Formula (XLVII):



XLVII

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

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

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$,

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

$-Z-Ar'-R_5$, and

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

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

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

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

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

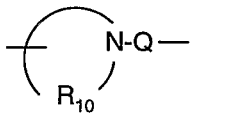
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

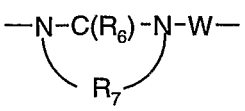
$-C(R_6)-N(R_8)-$,

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

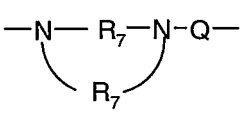
$-C(R_6)-N(OR_9)-$,



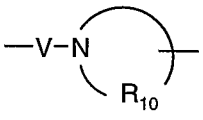
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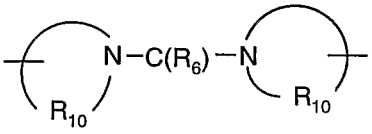
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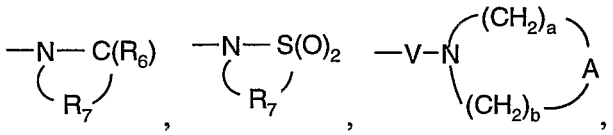


;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

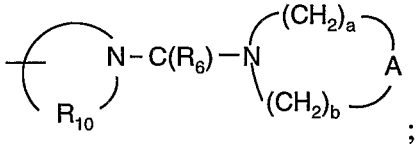
each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl,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

each R_5 is independently selected from the group consisting of:


,

,

,


and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, 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 $-C(R_6)-N(OR_9)-$;

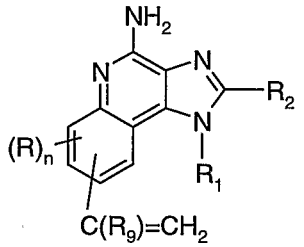
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

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 $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

79. A compound of formula (XLVIII):



XLVIII

wherein:

R is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

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

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

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

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

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

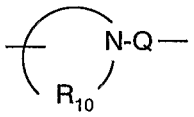
-O-C(O)-O-,

-$N(R_8)$-Q-,

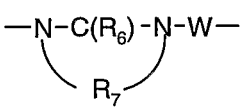
-$C(R_6)$-$N(R_8)$-,

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

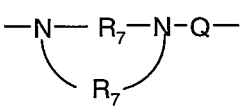
-$C(R_6)$-$N(OR_9)$-,



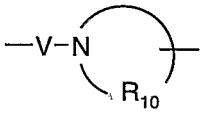
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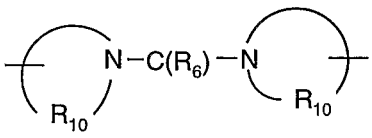
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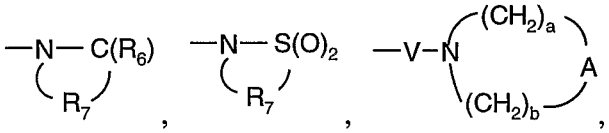


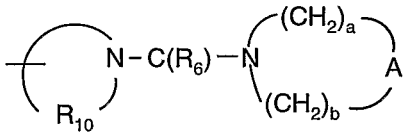
;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:





and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, 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 $-C(R_6)-N(OR_9)$-;

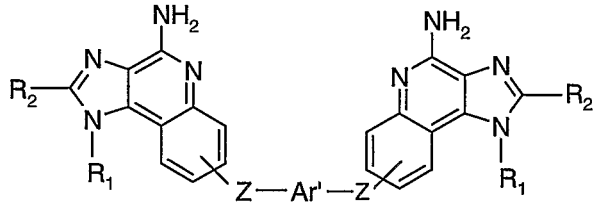
V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

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.

80. A compound of formula (XLVI):



XLVI

wherein:

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

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

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

each X is independently 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 with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently 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)-,

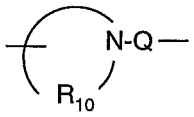
-O-C(O)-O-,

-N(R_8)-Q-,

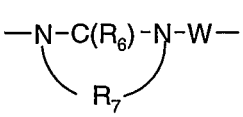
-C(R_6)-N(R_8)-,

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

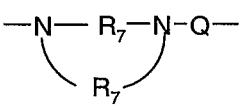
-C(R_6)-N(OR_9)-,



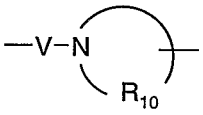
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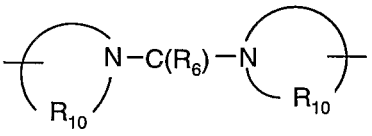
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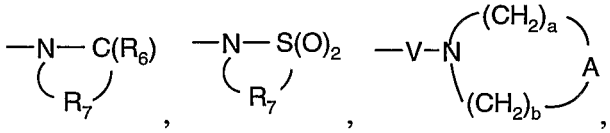
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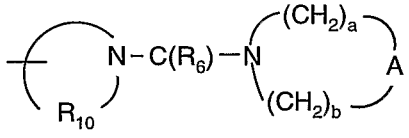
each Z is independently selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

each R_4 is independently 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;

each R_5 is independently selected from the group consisting of:





and ;

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

each R_7 is independently C_{2-7} alkylene;

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

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

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

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, 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 $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

81. The compound or salt of claim 80 wherein the compound or salt induces the biosynthesis of one or more cytokines.

82. The compound or salt of claim 80 wherein the compound or salt inhibits the biosynthesis of TNF.

83. The compound or salt of claim 80 wherein Z is a bond.

84. The compound or salt of claim 80 wherein Ar' is phenylene.

85. The compound or salt of claim 80 wherein R_1 is selected from the group consisting of alkyl, hydroxyalkyl, and -X-Y-R_4 wherein X is alkylene, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)-, and R_4 is alkyl.

86. The compound or salt of claim 80 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

87. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 1 and a pharmaceutically acceptable carrier.

88. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 10 and a pharmaceutically acceptable carrier.

89. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 21 and a pharmaceutically acceptable carrier.

90. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 37 and a pharmaceutically acceptable carrier.

91. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 44 and a pharmaceutically acceptable carrier.

92. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 51 and a pharmaceutically acceptable carrier.

93. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 58 and a pharmaceutically acceptable carrier.

94. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 65 and a pharmaceutically acceptable carrier.

95. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 71 and a pharmaceutically acceptable carrier.

96. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 80 and a pharmaceutically acceptable carrier.

97. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 2 to the animal.

98. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 11 to the animal.

99. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 22 to the animal.

100. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 38 to the animal.

101. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 45 to the animal.

102. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 52 to the animal.

103. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 59 to the animal.

104. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 66 to the animal.

105. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 72 to the animal.

106. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 81 to the animal.

107. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 3 to the animal.

108. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 12 to the animal.

109. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 23 to the animal.

110. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 39 to the animal.

111. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 46 to the animal.

112. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 53 to the animal.

113. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 60 to the animal.

114. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 67 to the animal.

115. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 73 to the animal.

116. A method of inhibiting the biosynthesis of TNF in an animal comprising administering an effective amount of a compound or salt of claim 82 to the animal.

117. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 2 to the animal.

118. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 11 to the animal.

119. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 22 to the animal.

120. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 38 to the animal.

121. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 45 to the animal.

122. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 52 to the animal.

123. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 59 to the animal.

124. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 66 to the animal.

125. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 72 to the animal.

126. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of claim 81 to the animal.

127. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 2 to the animal.

128. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 11 to the animal.

129. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 22 to the animal.

130. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 38 to the animal.

131. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 45 to the animal.

132. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 52 to the animal.

133. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 59 to the animal.

134. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 66 to the animal.

135. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 72 to the animal.

136. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of claim 81 to the animal.