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(71) Applicant *(for all designated States except US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GmbH** [DE/DE]; Binger Strasse 173, 55216 Ingelheim (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TSANTRIZOS, Youla S.** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **BAILEY, Murray D.** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **BILODEAU, François** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **CARSON, Rebekah J.** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **FADER, Lee** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **HALMOS, Teddy** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **KAWAI, Stephen** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **LANDRY, Serge** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **LAPLANTE, Steven** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). **SIMONEAU, Bruno** [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA).

(74) Agent: **LOOPER, Ywe J.**; c/o Boehringer Ingelheim (Canada) Ltd., 2100 Cunard Street, Laval, Québec H7S 2G5 (CA).

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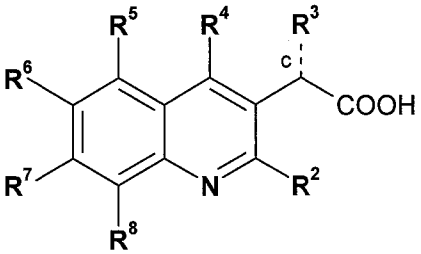

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(57) Abstract: Compounds of formula I : wherein c, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are defined herein, are useful as inhibitors of HIV replication.

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INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION

RELATED APPLICATIONS

This application claims benefit of U.S. Serial No. 60/988327, filed November 15, 2007, which is herein incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods for the treatment of human immunodeficiency virus (HIV) infection. In particular, the present invention provides novel inhibitors of HIV replication, pharmaceutical compositions containing such compounds and methods for using these compounds in the treatment of HIV infection. More specifically, the present invention provides novel inhibitors of the HIV integrase enzyme, pharmaceutical compositions containing such compounds and methods for using these compounds to reduce HIV replication and in the treatment of HIV infection.

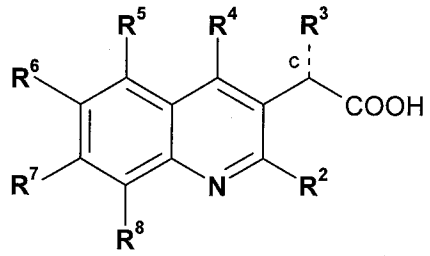
BACKGROUND OF THE INVENTION

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), particularly the HIV-1 strain. Most currently approved therapies for HIV infection target the viral reverse transcriptase and protease enzymes. There is additionally one approved drug targeting gp41 to inhibit viral entry and one approved drug targeting the integrase enzyme. Within the reverse transcriptase inhibitor and protease inhibitor classes, resistance of HIV to existing drugs is a problem. Therefore, it is important to discover and develop new antiretroviral compounds.

SUMMARY OF THE INVENTION

The present invention provides a novel series of compounds having inhibitory activity against HIV replication. Furthermore, representative compounds of the invention have activity as inhibitors in a cell-based HIV replication assay. Further objects of this invention arise for the one skilled in the art from the following description and the examples. The compounds of the present invention have an affinity for the HIV integrase enzyme. Therefore, the compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.

One aspect of the invention provides an isomer, racemate, enantiomer or diastereomer of a compound of formula (I):



(I)

wherein

R^2 is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl, **Het**, halo, nitro or cyano;

b) -C(=O)-R^{11}, -C(=O)-O-R^{11}, -S-R^{11}, -SO-R^{11}, -SO_2-R^{11}, -(C_{1-6})alkylene-R^{11}, -(C_{1-6})alkylene-C(=O)-R^{11}, -(C_{1-6})alkylene-C(=O)-O-R^{11}, -(C_{1-6})alkylene-O-R^{11}, –(C_{1-6})alkylene-S-R^{11}, -(C_{1-6})alkylene-SO-R^{11} or -(C_{1-6})alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;
and
wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -$SO_2$$(C_{1-6})$alkyl, -C(=O)-$NH_2$, -C(=O)-NH$(C_{1-4})$alkyl, -C(=O)-N$((C_{1-4})alkyl)_2$, -C(=O)-aryl, --C(=O)-**Het**, NH_2, -NH(C_{1-6})alkyl and -N$((C_{1-6})alkyl)_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

c) -O-R^{8a}

wherein R^{8a} is selected from H, (C_{2-6})alkenyl, (C_{2-6})alkynyl,

(C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

d) $-N(\mathbf{R^9})\mathbf{R^{10}}$, $-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-O-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-SO_2-N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene-$N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene-$C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene$-O-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, or $-(C_{1-6})$alkylene-$SO_2-N(\mathbf{R^9})\mathbf{R^{10}}$ wherein

$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$\mathbf{R^{11}}$, $-SO_2-\mathbf{R^{11}}$, $-C(=O)-\mathbf{R^{11}}$, $-C(=O)O\mathbf{R^{11}}$ and $-C(=O)N(\mathbf{R^9})\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above; or

$\mathbf{R^2}$ may also be H, (C_{1-6})alkyl or $-O-(C_{1-6})$alkyl when one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when one of $\mathbf{R^6}$ or $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl,

$\mathbf{R^5}$ and $\mathbf{R^8}$ are each independently selected from:

a) halo, nitro or cyano;

b) $\mathbf{R^{11}}$, $-C(=O)-\mathbf{R^{11}}$, $-C(=O)-O-\mathbf{R^{11}}$, $-O-\mathbf{R^{11}}$, $-S-\mathbf{R^{11}}$, $-SO-\mathbf{R^{11}}$, $-SO_2-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$C(=O)-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$C(=O)-O-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$O-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$S-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$SO-\mathbf{R^{11}}$ or $-(C_{1-6})$alkylene-$SO_2-\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, $-O(C_{1-6})$alkyl, $-O(C_{1-6})$haloalkyl, -SH, $-S(C_{1-6})$alkyl, $-SO(C_{1-6})$alkyl, $-SO_2(C_{1-6})$alkyl, $-C(=O)-NH_2$, $-C(=O)-NH(C_{1-4})$alkyl, $-C(=O)-N((C_{1-4})\text{alkyl})_2$, -C(=O)-aryl, -C(=O)-**Het**, NH_2, $-NH(C_{1-6})$alkyl and $-N((C_{1-6})\text{alkyl})_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, $-O-(C_{1-6})$haloalkyl, or $-O-(C_{1-6})$alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

c) $-N(R^9)R^{10}$, $-C(=O)-N(R^9)R^{10}$, $-O-C(=O)-N(R^9)R^{10}$, $-SO_2-N(R^9)R^{10}$, $-(C_{1-6})$alkylene-$N(R^9)R^{10}$, $-(C_{1-6})$alkylene-$C(=O)-N(R^9)R^{10}$, $-(C_{1-6})$alkylene$-O-C(=O)-N(R^9)R^{10}$, or $-(C_{1-6})$alkylene-$SO_2-N(R^9)R^{10}$ wherein

R^9 is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

R^{10} is in each instance independently selected from R^{11}, $-(C_{1-6})$alkylene-R^{11}, $-SO_2-R^{11}$, $-C(=O)-R^{11}$, $-C(=O)OR^{11}$ and $-C(=O)N(R^9)R^{11}$; wherein R^{11} and R^9 are as defined above;

R^6 is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) $-C(=O)-R^{11}$, $-C(=O)-O-R^{11}$, $-O-R^{11}$, $-S-R^{11}$, $-SO-R^{11}$, $-SO_2-R^{11}$, $-(C_{1-6})$alkylene-R^{11}, $-(C_{1-6})$alkylene-$C(=O)-R^{11}$, $-(C_{1-6})$alkylene-$C(=O)-O-R^{11}$, $-(C_{1-6})$alkylene-$O-R^{11}$, $-(C_{1-6})$alkylene-$S-R^{11}$, $-(C_{1-6})$alkylene-$SO-R^{11}$ or $-(C_{1-6})$alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

c) $-N(R^9)R^{10}$, $-C(=O)-N(R^9)R^{10}$, $-O-C(=O)-N(R^9)R^{10}$, $-SO_2-N(R^9)R^{10}$, $-(C_{1-6})$alkylene-$N(R^9)R^{10}$, $-(C_{1-6})$alkylene-$C(=O)-N(R^9)R^{10}$, $-(C_{1-6})$alkylene$-O-C(=O)-N(R^9)R^{10}$, or $-(C_{1-6})$alkylene-$SO_2-N(R^9)R^{10}$ wherein

R^9 is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

R^{10} is in each instance independently selected from R^{11}, $-(C_{1-6})$alkylene-R^{11}, $-SO_2-R^{11}$, $-C(=O)-R^{11}$, $-C(=O)OR^{11}$ and $-C(=O)N(R^9)R^{11}$; wherein R^{11} and R^9 are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, $-O(C_{1-6})$alkyl, $-O(C_{1-6})$haloalkyl, -SH, $-S(C_{1-6})$alkyl, $-SO(C_{1-6})$alkyl, $-SO_2(C_{1-6})$alkyl, $-NH_2$, $-NH(C_{1-6})$alkyl and $-N((C_{1-6})alkyl)_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

R^6 may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl;

R^7 is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) -C(=O)-R^{11}, -C(=O)-O-R^{11}, -O-R^{11}, -S-R^{11}, -SO-R^{11}, -SO_2-R^{11}, -(C_{1-6})alkylene-R^{11}, -(C_{1-6})alkylene-C(=O)-R^{11}, -(C_{1-6})alkylene-C(=O)-O-R^{11}, -(C_{1-6})alkylene-O-R^{11}, –(C_{1-6})alkylene-S-R^{11}, -(C_{1-6})alkylene-SO-R^{11} or -(C_{1-6})alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

c) -N(R^9)R^{10}, –C(=O)-N(R^9)R^{10}, –O-C(=O)-N(R^9)R^{10}, –SO_2-N(R^9)R^{10}, -(C_{1-6})alkylene-N(R^9)R^{10}, -(C_{1-6})alkylene-C(=O)-N(R^9)R^{10}, -(C_{1-6})alkylene–O-C(=O)-N(R^9)R^{10}, or -(C_{1-6})alkylene-SO_2-N(R^9)R^{10} wherein

R^9 is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

R^{10} is in each instance independently selected from R^{11}, -(C_{1-6})alkylene-R^{11}, -SO_2-R^{11}, -C(=O)-R^{11}, -C(=O)OR^{11} and -C(=O)N(R^9)R^{11}; wherein R^{11} and R^9 are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -$SO_2$$(C_{1-6})$alkyl, -$NH_2$, -NH$(C_{1-6})$alkyl and -N$((C_{1-6})$alkyl$)_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

R^7 may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of R^5 or R^8 is other than H or when R^6 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl;

or R^5 and R^6, together with the C to which they are attached, R^6 and R^7, together with the C to which they are attached, or R^7 and R^8, together with the C to which they are attached; may be linked to form a 5- or 6-membered carbocycle or a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2;

wherein the carbocycle or heterocycle is optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})\text{alkyl})_2$;

R^3 is (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl-, **Het**-(C_{1-6})alkyl- or -**Y**-R^{31}, and bond **c** is a single bond; or

R^3 is (C_{1-6})alkylidene and bond **c** is a double bond;

wherein **Y** is O or S and R^{31} is (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, aryl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl- or **Het**-(C_{1-6})alkyl-;

wherein each of the (C_{1-6})alkylidene, (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl-, **Het**-(C_{1-6})alkyl- and -**Y**-R^{31} is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, halo, cyano, oxo and -O(C_{1-6})alkyl;

R^4 is aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with 1 to 5 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})\text{alkyl})_2$; wherein the (C_{1-6})alkyl is optionally substituted with hydroxy, -O(C_{1-6})alkyl, cyano or oxo;

wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2;

or a salt or an ester thereof.

Another aspect of this invention provides a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, as a medicament.

Still another aspect of this invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof; and one or more pharmaceutically acceptable carriers.

According to an embodiment of this aspect, the pharmaceutical composition according to this invention additionally comprises at least one other antiviral agent.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of an HIV infection in a mammal having or at risk of having the infection.

A further aspect of the invention involves a method of treating an HIV infection in a mammal having or at risk of having the infection, the method comprising administering to the mammal a therapeutically effective amount of a compound of formula (I), a pharmaceutically acceptable salt or ester thereof, or a composition thereof as described hereinabove.

Another aspect of the invention involves a method of treating an HIV infection in a mammal having or at risk of having the infection, the method comprising administering to the mammal a therapeutically effective amount of a combination of

a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, and at least one other antiviral agent; or a composition thereof.

Also within the scope of this invention is the use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt or ester thereof, for the treatment of an HIV infection in a mammal having or at risk of having the infection.

Another aspect of this invention provides the use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament for the treatment of an HIV infection in a mammal having or at risk of having the infection.

An additional aspect of this invention refers to an article of manufacture comprising a composition effective to treat an HIV infection; and packaging material comprising a label which indicates that the composition can be used to treat infection by HIV; wherein the composition comprises a compound of formula (I) according to this invention or a pharmaceutically acceptable salt or ester thereof.

Still another aspect of this invention relates to a method of inhibiting the replication of HIV comprising exposing the virus to an effective amount of the compound of formula (I), or a salt or ester thereof, under conditions where replication of HIV is inhibited.

Further included in the scope of the invention is the use of a compounds of formula (I) to inhibit the activity of the HIV integrase enzyme.

Further included in the scope of the invention is the use of a compound of formula (I), or a salt or ester thereof, to inhibit the replication of HIV.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

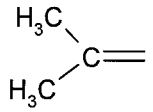
As used herein, the following definitions apply unless otherwise noted:

The term "substituent", as used herein and unless specified otherwise, is intended to mean an atom, radical or group which may be bonded to a carbon atom, a

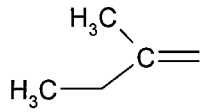
heteroatom or any other atom which may form part of a molecule or fragment thereof, which would otherwise be bonded to at least one hydrogen atom. Substituents contemplated in the context of a specific molecule or fragment thereof are those which give rise to chemically stable compounds, such as are recognized by those skilled in the art.

The term "(C_{1-n})alkyl" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean acyclic, straight or branched chain alkyl radicals containing from 1 to n carbon atoms. "(C_{1-6})alkyl" includes, but is not limited to, methyl, ethyl, propyl (*n*-propyl), butyl (*n*-butyl), 1-methylethyl (*iso*-propyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), pentyl and hexyl. The abbreviation Me denotes a methyl group; Et denotes an ethyl group, Pr denotes a propyl group, iPr denotes a 1-methylethyl group, Bu denotes a butyl group and tBu denotes a 1,1-dimethylethyl group.

The term "(C_{1-n})alkylidene" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean acyclic, straight or branched chain alkyl radicals containing from 1 to n carbon atoms which are bonded to a molecule or fragment thereof, as a substituent thereof, by a double bond. "(C_{1-6})alkylidene" includes, but is not limited to, CH_2=, CH_3CH=, CH_3CH_2CH=,

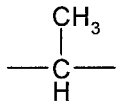
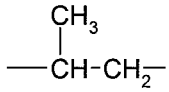
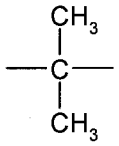


and



groups. Unless specified otherwise, the term "(C_{2-n})alkylidene" is understood to encompass individual stereoisomers where possible, including but not limited to (*E*) and (*Z*) isomers, and mixtures thereof. When a (C_{2-n})alkylidene group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "(C_{1-n})alkylene" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean acyclic, straight or branched chain divalent alkyl radicals containing from 1 to n carbon atoms. "(C_{1-6})alkylene"

includes, but is not limited to, $-CH_2-$, $-CH_2CH_2-$,  ,  and  .

The term "(C_{2-n})alkenyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a double bond. Examples of such radicals include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl, and 1-butenyl. Unless specified otherwise, the term "(C_{2-n})alkenyl" is understood to encompass individual stereoisomers where possible, including but not limited to (*E*) and (*Z*) isomers, and mixtures thereof. When a (C_{2-n})alkenyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "(C_{2-n})alkynyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a triple bond. Examples of such radicals include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butynyl. When a (C_{2-n})alkynyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "(C_{3-m})cycloalkyl" as used herein, wherein m is an integer, either alone or in combination with another radical, is intended to mean a cycloalkyl substituent containing from 3 to m carbon atoms and includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "(C_{3-m})cycloalkyl-(C_{1-n})alkyl-" as used herein, wherein n and m are both integers, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a cycloalkyl radical containing from 3 to m carbon atoms as defined above. Examples of (C_{3-7})cycloalkyl-(C_{1-6})alkyl- include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclobutylethyl, 2-cyclobutylethyl, 1-cyclopentylethyl, 2-cyclopentylethyl, 1-cyclohexylethyl and 2-cyclohexylethyl. When a (C_{3-m})cycloalkyl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the cycloalkyl or the alkyl portion thereof or both, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "aryl" as used herein, either alone or in combination with another radical, is intended to mean a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, 1-naphthyl, 2-naphthyl, tetrahydronaphthyl and dihydronaphthyl.

The term "aryl-(C_{1-n})alkyl-" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with an aryl radical as defined above. Examples of aryl-(C_{1-n})alkyl- include, but are not limited to, phenylmethyl (benzyl), 1-phenylethyl, 2-phenylethyl and phenylpropyl. When an aryl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the aryl or the alkyl portion thereof or both, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "carbocycle" as used herein, either alone or in combination with another radical, is intended to mean a cyclic compound, either aromatic or non-aromatic, saturated or unsaturated, in which all of the ring members are carbon atoms. The carbocycle group may containing 5 or 6 carbon atom and may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or

unsaturated.

The term "**Het**" as used herein, either alone or in combination with another radical, is intended to mean a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, unless specified otherwise; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2. When a **Het** group is substituted, it is understood that substituents may be attached to any carbon atom or heteroatom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "**Het**-(C_{1-n})alkyl-" as used herein and unless specified otherwise, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a **Het** substituent as defined above. Examples of **Het**-(C_{1-n})alkyl- include, but are not limited to, thienylmethyl, furylmethyl, piperidinylethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, quinolinylpropyl, and the like. When an **Het**-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the **Het** or the alkyl portion thereof or both, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "heteroatom" as used herein is intended to mean O, S or N.

The term "heterocycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a 3- to 7-membered saturated, unsaturated or aromatic heterocycle containing from 1 to 4 heteroatoms each independently selected from O, N and S; or a monovalent radical derived by removal of a hydrogen atom therefrom. Examples of such heterocycles include, but

are not limited to, azetidine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, thiazolidine, oxazolidine, pyrrole, thiophene, furan, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, tetrazole, piperidine, piperazine, azepine, diazepine, pyran, 1,4-dioxane, 4-morpholine, 4-thiomorpholine, pyridine, pyridine-N-oxide, pyridazine, pyrazine and pyrimidine, and saturated, unsaturated and aromatic derivatives thereof.

The term "heteropolycycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a heterocycle as defined above fused to one or more other cycle, including a carbocycle, a heterocycle or any other cycle; or a monovalent radical derived by removal of a hydrogen atom therefrom. Examples of such heteropolycycles include, but are not limited to, indole, isoindole, benzimidazole, benzothiophene, benzofuran, benzopyran, benzodioxole, benzodioxane, benzothiazole, quinoline, isoquinoline, and naphthyridine, and saturated, unsaturated and aromatic derivatives thereof.

The term "halo" as used herein is intended to mean a halogen substituent selected from fluoro, chloro, bromo or iodo.

The term "(C_{1-n})haloalkyl" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above wherein one or more hydrogen atoms are each replaced by a halo substituent. Examples of (C_{1-n})haloalkyl include but are not limited to chloromethyl, chloroethyl, dichloroethyl, bromomethyl, bromoethyl, dibromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl and difluoroethyl.

The terms "-O-(C_{1-n})alkyl" or "(C_{1-n})alkoxy" as used herein interchangeably, wherein n is an integer, either alone or in combination with another radical, is intended to mean an oxygen atom further bonded to an alkyl radical having 1 to n carbon atoms as defined above. Examples of -O-(C_{1-n})alkyl include but are not limited to methoxy (CH_3O-), ethoxy (CH_3CH_2O-), propoxy ($CH_3CH_2CH_2O$-), 1-methylethoxy (*iso*-propoxy; $(CH_3)_2CH$-O-) and 1,1-dimethylethoxy (*tert*-butoxy; $(CH_3)_3C$-O-). When an -O-(C_{1-n})alkyl radical is substituted, it is understood to be substituted on the (C_{1-n})alkyl portion thereof, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "-O-(C_{1-n})haloalkyl", wherein n is an integer, either alone or in combination with another radical, is intended to mean an oxygen atom further bonded to a haloalkyl radical having 1 to n carbon atoms as defined above. When an -O-(C_{1-n})haloalkyl radical is substituted, it is understood to be substituted on the (C_{1-n})alkyl portion thereof.

The terms "-S-(C_{1-n})alkyl" or "(C_{1-n})alkylthio" as used herein interchangeably, wherein n is an integer, either alone or in combination with another radical, is intended to mean an sulfur atom further bonded to an alkyl radical having 1 to n carbon atoms as defined above. Examples of -S-(C_{1-n})alkyl include but are not limited to methylthio (CH_3S-), ethylthio (CH_3CH_2S-), propylthio ($CH_3CH_2CH_2S$-), 1-methylethylthio (*iso*propylthio; $(CH_3)_2CH$-S-) and 1,1-dimethylethylthio (*tert*-butylthio; $(CH_3)_3C$-S-). When -S-(C_{1-n})alkyl radical, or an oxidized derivative thereof, such as an -SO-(C_{1-n})alkyl radical or an -SO_2-(C_{1-n})alkyl radical, is substituted, each is understood to be substituted on the (C_{1-n})alkyl portion thereof, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "oxo" as used herein is intended to mean an oxygen atom attached to a carbon atom as a substituent by a double bond (=O).

The term "thioxo" as used herein is intended to mean a sulfur atom attached to a carbon atom as a substituent by a double bond (=S).

The term "cyano" as used herein is intended to mean a carbon atom attached to a nitrogen atom as a substituent by a triple bond.

The term "COOH" as used herein is intended to mean a carboxyl group (-C(=O)-OH). It is well known to one skilled in the art that carboxyl groups may be substituted by functional group equivalents. Examples of such functional group equivalents contemplated in this invention include, but are not limited to, esters, amides, imides, boronic acids, phosphonic acids, phosphoric acids, tetrazoles, triazoles, N-acylsulfamides ($RCONHSO_2NR_2$), and N-acylsulfonamides ($RCONHSO_2R$).

The term "functional group equivalent" as used herein is intended to mean an atom or group that may replace another atom or group which has similar electronic, hybridization or bonding properties.

The term "protecting group" as used herein is intended to mean protecting groups that can be used during synthetic transformation, including but not limited to examples which are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981), and more recent editions thereof, herein incorporated by reference.

The following designation  is used in sub-formulas to indicate the bond which is connected to the rest of the molecule as defined.

The term "salt thereof" as used herein is intended to mean any acid and/or base addition salt of a compound according to the invention, including but not limited to a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable salt" as used herein is intended to mean a salt of a compound according to the invention which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, for example, S.M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19, herein incorporated by reference.

The term "pharmaceutically-acceptable acid addition salt" as used herein is intended to mean those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid and the like, and organic acids including but not limited to acetic acid, trifluoroacetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, butyric acid, camphoric acid,

camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethanesulfonic acid (isethionic acid), lactic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid, 2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid and the like.

The term "pharmaceutically-acceptable base addition salt" as used herein is intended to mean those salts which retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases including but not limited to ammonia or the hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include but are not limited to salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

The term "ester thereof" as used herein is intended to mean any ester of a compound according to the invention in which any of the -COOH substituents of the

molecule is replaced by a -COOR substituent, in which the **R** moiety of the ester is any carbon-containing group which forms a stable ester moiety, including but not limited to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, each of which being optionally further substituted. The term "ester thereof" includes but is not limited to pharmaceutically acceptable esters thereof.

The term "pharmaceutically acceptable ester" as used herein is intended to mean esters of the compound according to the invention in which any of the COOH substituents of the molecule are replaced by a -COOR substituent, in which the **R** moiety of the ester is selected from alkyl (including, but not limited to, methyl, ethyl, propyl, 1-methylethyl, 1,1-dimethylethyl, butyl); alkoxyalkyl (including, but not limited to methoxymethyl); acyloxyalkyl (including, but not limited to acetoxymethyl); arylalkyl (including, but not limited to, benzyl); aryloxyalkyl (including, but not limited to, phenoxymethyl); and aryl (including, but not limited to phenyl) optionally substituted with halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy. Other suitable esters can be found in Design of Prodrugs, Bundgaard, H. Ed. Elsevier (1985), herein incorporated by reference. Such pharmaceutically acceptable esters are usually hydrolyzed *in vivo* when injected into a mammal and transformed into the acid form of the compound according to the invention. With regard to the esters described above, unless otherwise specified, any alkyl moiety present preferably contains 1 to 16 carbon atoms, more preferably 1 to 6 carbon atoms. Any aryl moiety present in such esters preferably comprises a phenyl group. In particular the esters may be a (C_{1-16})alkyl ester, an unsubstituted benzyl ester or a benzyl ester substituted with at least one halogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, nitro or trifluoromethyl.

The term "mammal" as used herein is intended to encompass humans, as well as non-human mammals which are susceptible to infection by HIV. Non-human mammals include but are not limited to domestic animals, such as cows, pigs, horses, dogs, cats, rabbits, rats and mice, and non-domestic animals.

The term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but

before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life.

The term "antiviral agent" as used herein is intended to mean an agent that is effective to inhibit the formation and/or replication of a virus in a mammal, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal.

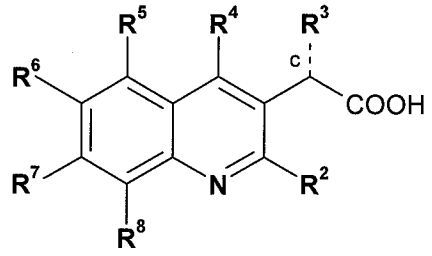
The term "inhibitor of HIV replication" as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro, ex vivo* or *in vivo*.

The term "HIV integrase" or "integrase", used herein interchangeably, means the integrase enzyme encoded by the human immunodeficiency virus type 1.

The term "therapeutically effective amount" means an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

Preferred embodiments

In the following preferred embodiments, groups and substituents of the compounds of formula (I):

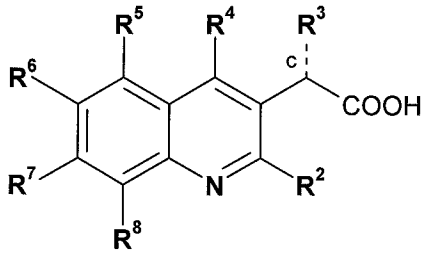


(I)

according to this invention are described in detail.

Core:

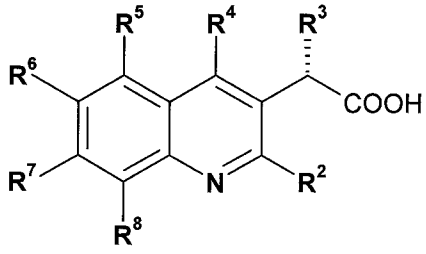
Core-A: In one embodiment, the compounds of the invention are represented by formula (Ia):



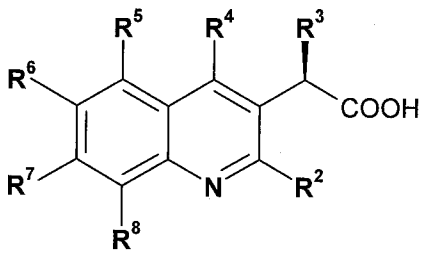
(Ia)

wherein **c**, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

It will be apparent to a person skilled in the art that, when bond **c** is a single bond, the carbon atom bonded to the –COOH and R^3 substituents can exist in two possible stereochemical configurations, as shown in formulas (Ib) and (Ic) below:



(Ib)

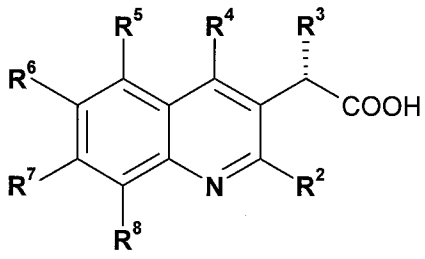


(Ic)

wherein R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

It has been found that compounds of formula (Ib) have improved activity over compounds of formula (Ic).

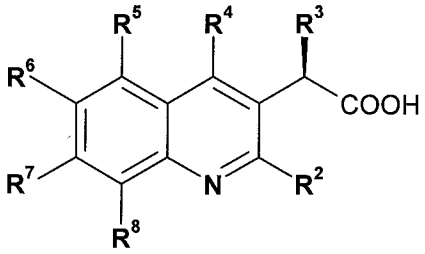
Core-B: In one embodiment, the compounds of the invention are represented by formula (Ib):



(Ib)

wherein R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

Core-C: In an alternative embodiment, the compounds of the invention are represented by formula (Ic):



(Ic)

wherein R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

Any and each individual definition of the **Core** as set out herein may be combined with any and each individual definition of R^2, R^3, R^4, R^5, R^6, R^7 and R^8 as set out herein.

R^2:

R^2-A: In one embodiment, R^2 is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl, **Het**, halo, nitro or cyano;

b) $-C(=O)-R^{11}$, $-C(=O)-O-R^{11}$, $-S-R^{11}$, $-SO-R^{11}$, $-SO_2-R^{11}$, $-(C_{1-6})$alkylene-R^{11}, $-(C_{1-6})$alkylene-$C(=O)-R^{11}$, $-(C_{1-6})$alkylene-$C(=O)-O-R^{11}$, $-(C_{1-6})$alkylene-$O-R^{11}$, $-(C_{1-6})$alkylene-$S-R^{11}$, $-(C_{1-6})$alkylene-$SO-R^{11}$ or $-(C_{1-6})$alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -$SO_2(C_{1-6})$alkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N$((C_{1-4})alkyl)_2$, -C(=O)-aryl, --C(=O)-**Het**, NH_2, -NH(C_{1-6})alkyl and -N$((C_{1-6})alkyl)_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

c) -O-$\mathbf{R^{8a}}$

wherein $\mathbf{R^{8a}}$ is selected from H, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

d) -N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –O-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –SO_2-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene–O-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, or -(C_{1-6})alkylene-SO_2-N($\mathbf{R^9}$)$\mathbf{R^{10}}$ wherein

$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -SO_2-$\mathbf{R^{11}}$, -C(=O)-$\mathbf{R^{11}}$, -C(=O)O$\mathbf{R^{11}}$ and -C(=O)N($\mathbf{R^9}$)$\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above; or

$\mathbf{R^2}$ may also be H, (C_{1-6})alkyl or -O-(C_{1-6})alkyl when one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when one of $\mathbf{R^6}$ or $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

$\mathbf{R^2}$-B: In analternative embodiment, $\mathbf{R^2}$ is (C_{1-6})alkyl or -O(C_{1-6})alkyl when one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when one of $\mathbf{R^6}$ or $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

$\mathbf{R^2}$-C: In another embodiment, $\mathbf{R^2}$ is (C_{1-6})alkyl when one of $\mathbf{R^5}$ and $\mathbf{R^8}$ is other than H or when one of $\mathbf{R^6}$ or $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

$\mathbf{R^2}$-D: In another embodiment, $\mathbf{R^2}$ is -CH_3 or -CH_2CH_3 when one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when one of $\mathbf{R^6}$ or $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl or

(C_{1-6})haloalkyl.

R^2-E: In another embodiment, R^2 is $-CH_3$ when one of R^5 or R^8 is other than H or when one of R^6 or R^7 is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

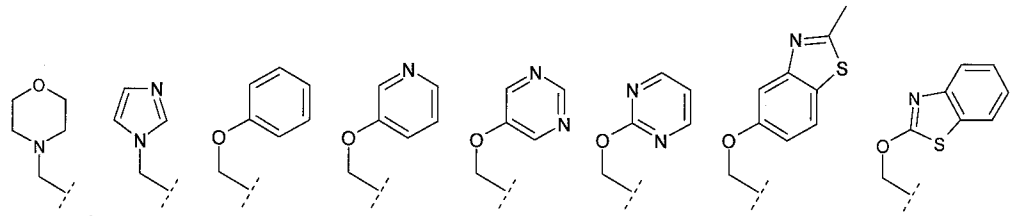
R^2-F: In another embodiment, R^2 is $-(C_{1-6})$alkylene-**Het**, $-(C_{1-6})$alkylene-aryl, $-(C_{1-6})$alkylene-O-**Het**, $-(C_{1-6})$alkylene-O-aryl, **Het** or aryl, all being optionally substituted with (C_{1-6})alkyl, (C_{1-6})haloalkyl, or $-O(C_{1-6})$alkyl.

R^2-G: In another embodiment, R^2 is $-(C_{1-6})$alkylene-**Het**, $-(C_{1-6})$alkylene-aryl, $-(C_{1-6})$alkylene-O-**Het** or $-(C_{1-6})$alkylene-O-aryl.

R^2-H: In another embodiment, R^2 is $-(C_{1-6})$alkylene-**Het**, $-(C_{1-6})$alkylene-aryl, $-(C_{1-6})$alkylene-O-**Het** or $-(C_{1-6})$alkylene-O-aryl; or

(C_{1-6})alkyl, when one of R^5 or R^8 is other than H or when one of R^6 or R^7 is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

R^2-I: In another embodiment, R^2 is



; or CH_3, when one of R^5 or R^8 is other than H or when one of R^6 or R^7 is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

Any and each individual definition of R^2 as set out herein may be combined with any and each individual definition of the **Core**, **c**, R^3, R^4, R^5, R^6, R^7 and R^8 as set out herein.

R^3:

R^3-A: In one embodiment, R^3 is (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl-, **Het**-(C_{1-6})alkyl- or -**Y**-R^{31}, and bond **c** is a single bond; or

R^3 is (C_{1-6})alkylidene and bond **c** is a double bond;

wherein **Y** is O or S and R^{31} is (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, aryl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl- or **Het**-(C_{1-6})alkyl-;

wherein each of the (C_{1-6})alkylidene, (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl,

(C_{2-6})alkynyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl-, **Het**-(C_{1-6})alkyl- and -**Y**-R^{31} is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, halo, cyano, oxo and -O(C_{1-6})alkyl.

R^3-B: In one embodiment, R^3 is (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl- or **Het**-(C_{1-6})alkyl-; wherein each of the (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl- and **Het**-(C_{1-6})alkyl- is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, halo, cyano, oxo and -O(C_{1-6})alkyl; and
bond **c** is a single bond.

R^3-C: In another embodiment, R^3 is (C_{1-6})alkyl or (C_{2-6})alkenyl; and
bond **c** is a single bond.

R^3-D: In an alternative embodiment, R^3 is -**Y**-(C_{1-6})alkyl, -**Y**-(C_{1-6})haloalkyl, -**Y**-(C_{2-6})alkenyl, -**Y**-(C_{2-6})alkynyl, -**Y**-(C_{3-7})cycloalkyl, -**Y**-aryl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-**Y**-, aryl-(C_{1-6})alkyl-**Y**- or **Het**-(C_{1-6})alkyl-**Y**-; wherein **Y** is O or S; and
wherein each of the -**Y**-(C_{1-6})alkyl, -**Y**-(C_{2-6})alkenyl, -**Y**-(C_{2-6})alkynyl, -**Y**-(C_{3-7})cycloalkyl, -**Y**-aryl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-**Y**-, aryl-(C_{1-6})alkyl-**Y**- and **Het**-(C_{1-6})alkyl-**Y**- is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, halo, cyano, oxo and -O(C_{1-6})alkyl; and
bond **c** is a single bond.

R^3-E: In another embodiment, R^3 is -O-(C_{1-6})alkyl, -O-(C_{1-6})haloalkyl, -O-(C_{2-6})alkenyl, -O-(C_{2-6})alkynyl, -O-(C_{3-7})cycloalkyl, -O-aryl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-O-, aryl-(C_{1-6})alkyl-O- or **Het**-(C_{1-6})alkyl-O-; wherein each of the -O-(C_{1-6})alkyl, -O-(C_{2-6})alkenyl, -O-(C_{2-6})alkynyl, -O-(C_{3-7})cycloalkyl, -O-aryl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-O-, aryl-(C_{1-6})alkyl-O- and **Het**-(C_{1-6})alkyl-O- is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, halo, cyano, oxo and -O(C_{1-6})alkyl; and
bond **c** is a single bond.

R^3-F: In another embodiment, R^3 is -O(C_{1-6})alkyl, -O-(C_{1-6})haloalkyl, -O-(C_{2-6})alkenyl, -O(C_{2-6})alkynyl, -O-(C_{3-7})cycloalkyl, -O-aryl, (C_{3-7})cycloalkyl-(C_{1-3})alkyl-O- or **Het**-(C_{1-3})alkyl-O-;

wherein **Het** is a 5- or 6-membered heterocycle having 1 to 3 heteroatoms each independently selected from N, O and S; and

wherein each of the -O(C_{1-6})alkyl, -O-(C_{3-7})cycloalkyl and **Het**-(C_{1-3})alkyl-O- is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-3})alkyl, cyano, oxo and -O(C_{1-6})alkyl; and

bond **c** is a single bond.

R^3-G: In another embodiment, **R^3** is -O(C_{1-6})alkyl, -O-(C_{1-6})haloalkyl, -O(C_{2-6})alkenyl, -O(C_{2-6})alkynyl or -O-(C_{3-7})cycloalkyl;

wherein each of the -O(C_{1-6})alkyl and -O-(C_{3-7})cycloalkyl is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-3})alkyl, cyano, oxo and -O(C_{1-6})alkyl; and

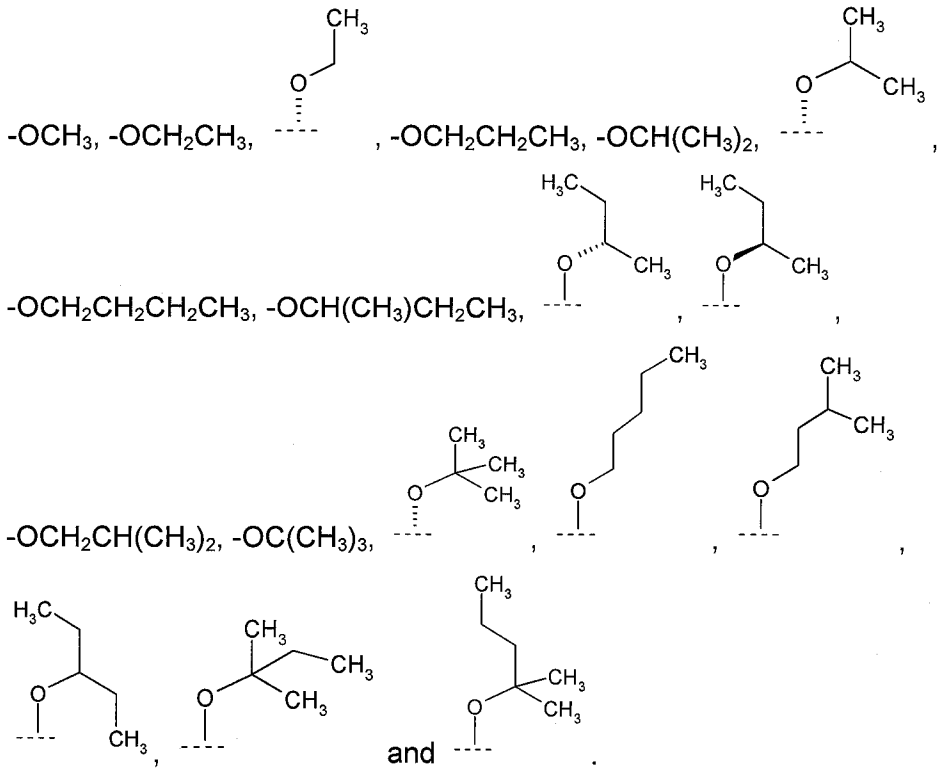
bond **c** is a single bond.

R^3-H: In another embodiment, **R^3** is -O(C_{1-4})alkyl; wherein the -O(C_{1-4})alkyl is optionally substituted with 1 to 2 substituents each independently selected from cyano, oxo and -O(C_{1-6})alkyl; and

bond **c** is a single bond.

R^3-I: In another embodiment, **R^3** is –OC(CH_3)$_3$; and bond **c** is a single bond.

R^3-J: In another embodiment, **R^3** is selected from:



Any and each individual definition of **c** and R^3 as set out herein may be combined with any and each individual definition of the **Core**, R^2, R^4, R^5, R^6, R^7 and R^8 as set out herein.

R^4:

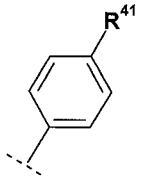
R^4-A: In one embodiment, R^4 is aryl optionally substituted with 1 to 5 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})alkyl)_2$; wherein the (C_{1-6})alkyl is optionally substituted with hydroxy, -O(C_{1-6})alkyl, cyano or oxo.

R^4-B: In another embodiment, R^4 is naphthyl or phenyl, wherein the phenyl is optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-4})alkyl, -SH, -S(C_{1-4})alkyl, $-NH_2$, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$; wherein the (C_{1-4})alkyl is optionally substituted with hydroxy, -O(C_{1-6})alkyl, cyano or oxo.

R^4-C: In another embodiment, R^4 is phenyl optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-4})alkyl and (C_{1-4})haloalkyl.

R^4-D: In another embodiment, R^4 is phenyl optionally substituted with 1 or 2 substituents each independently selected from F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$ and $-C(CH_3)_3$.

R^4-E: In another embodiment, R^4 is a group of formula:

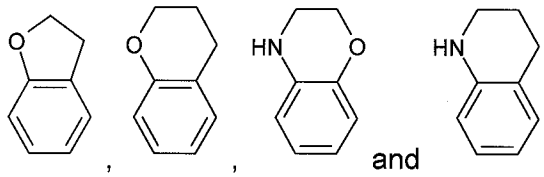


wherein R^{41} is selected from halo, (C_{1-4})alkyl and (C_{1-4})haloalkyl.

R^4-F: In an alternative embodiment, R^4 is **Het** optionally substituted with 1 to 4 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})alkyl)_2$; wherein the (C_{1-6})alkyl is optionally substituted with hydroxy, cyano or oxo.

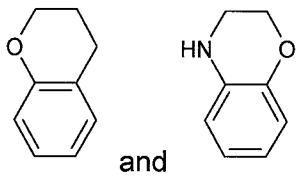
R^4-G: In another alternative embodiment, R^4 is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo and (C_{1-6})alkyl; wherein the **Het** is a 5- or 6-membered heterocycle having 1 to 3 heteroatoms each independently selected from N, O and S; or the **Het** is a 9- or 10-membered heteropolycycle having 1 to 3 heteroatoms each independently selected from N, O and S.

R^4-H: In another alternative embodiment, R^4 is Het optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl and $-O(C_{1-6})$alkyl;
wherein the Het is selected from:



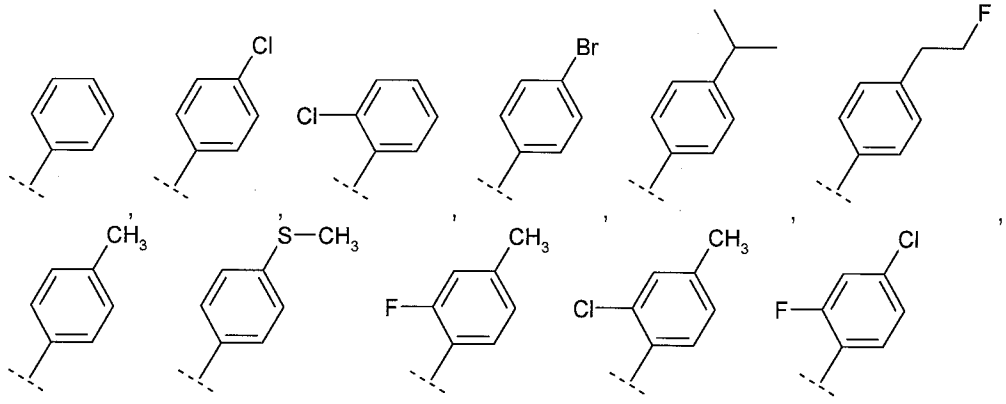
and .

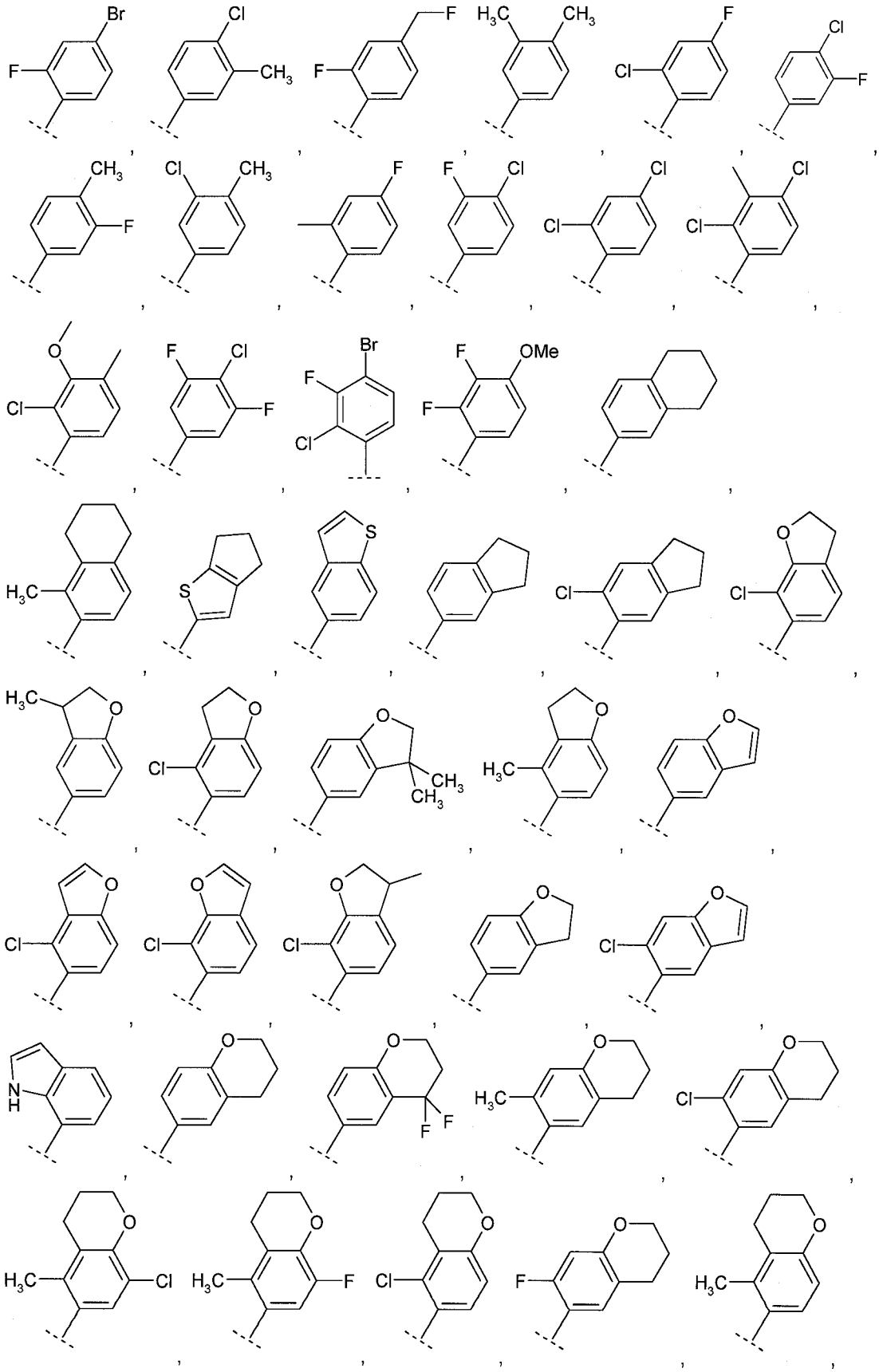
R^4-I: In another alternative embodiment, R^4 is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl and $-O(C_{1-6})$alkyl;
wherein the **Het** is selected from:

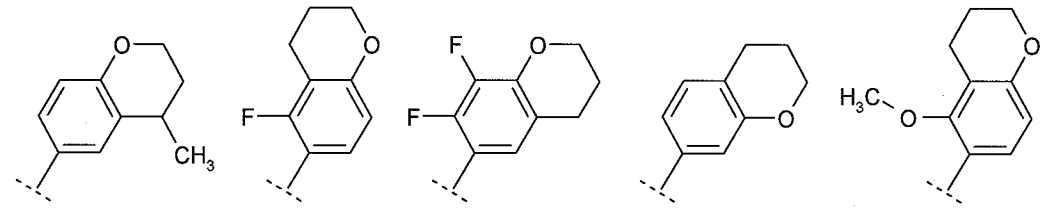
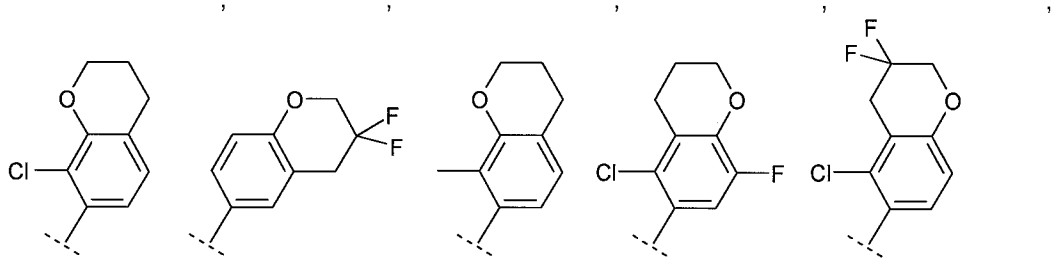
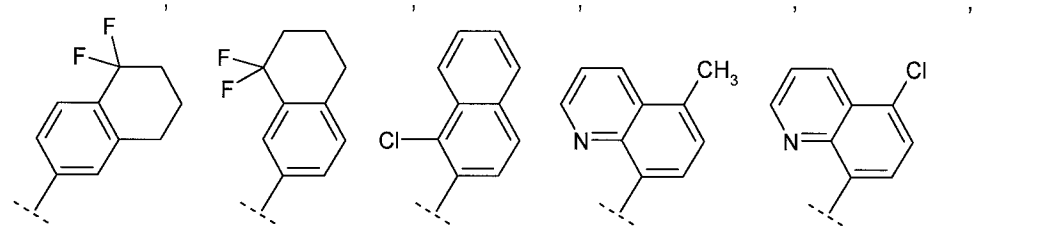
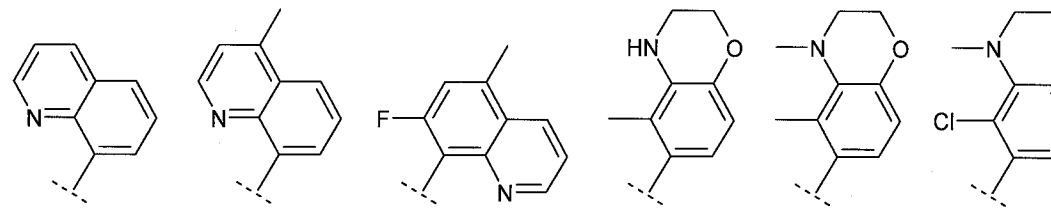
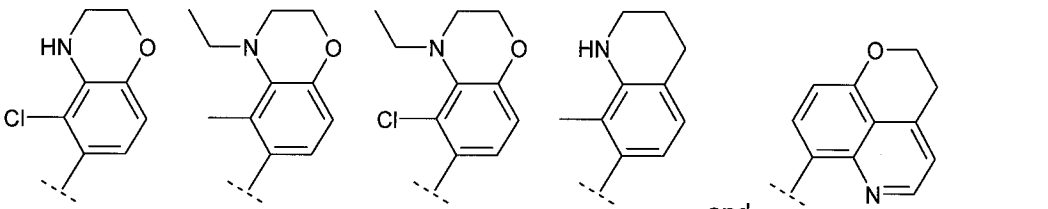


and .

R^4-J: In another alternative embodiment, R^4 is selected from:

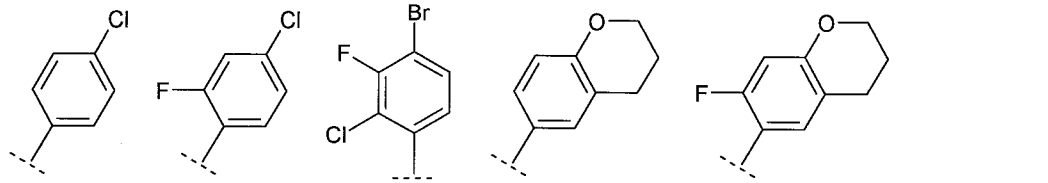
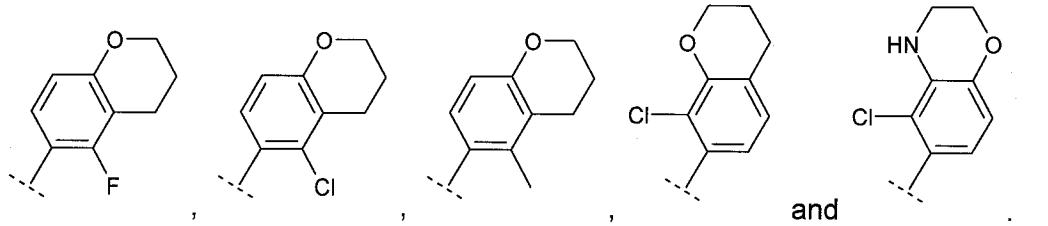




and

R^4-K: In another alternative embodiment, **R^4** is selected from:

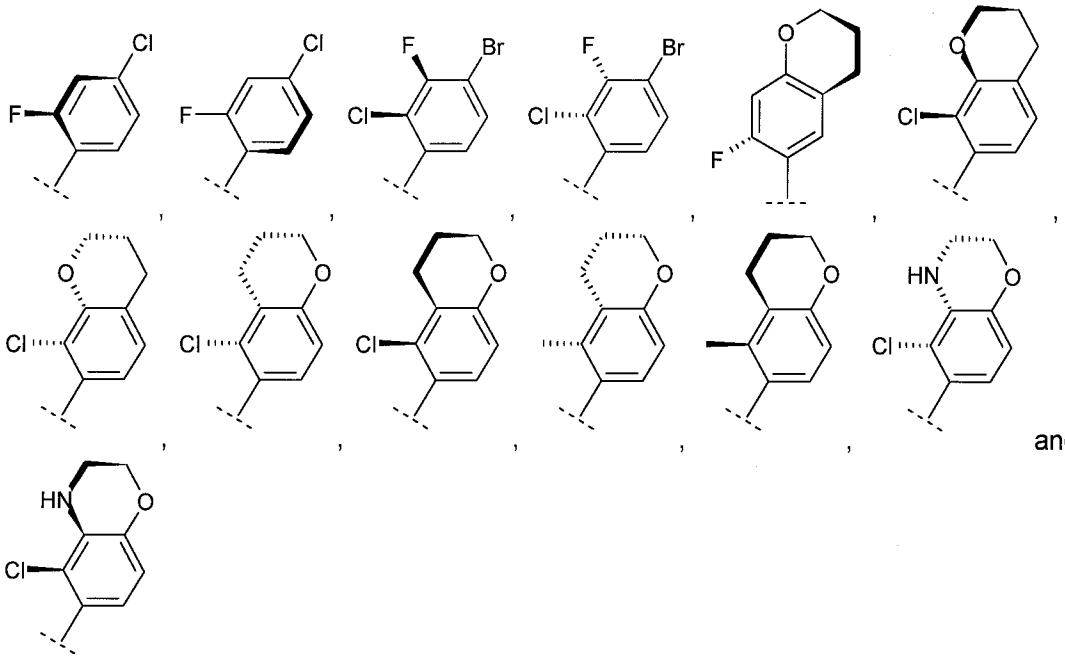



and

One skilled in the art will recognize that when the **R^4** substituent is not

symmetrically substituted about the axis of rotation of the bond attaching R^4 to **Core**, rotational isomers or atropisomers are possible. Compounds of the invention in which the R^4 substituent is not symmetrically substituted about the axis of rotation of the bond attaching R^4 to **Core** and in which the carbon atom bonded to the -COOH and R^3 substituents is chiral, as described above, will have two chiral centers, a chiral carbon atom and a rotational axis of asymmetry, and thus the atropisomers will exist as diastereomers. However, individual diastereomeric atropisomers may or may not be detectable and/or separable, depending upon the relative amounts of each atropisomer formed during synthesis, present at equilibrium, and the degree of steric hindrance to rotation about the C-4 chiral axis, and therefore, the rate at which interconversion between these atropoisomers occurs. Once separated, individual atropoisomers may be very stable or interconvert, rapidly or slowly, with each other to form an equilibrium mixture of atropoisomers.

R^4-L: In another alternative embodiment, R^4 is selected from:



and

Any and each individual definition of R^4 as set out herein may be combined with any and each individual definition of the **Core**, **c**, R^2, R^3, R^5, R^6, R^7 and R^8 as set out herein.

R^5:

R^5-A: In one embodiment, R^5 is selected from:

a) halo, nitro or cyano;

b) $\mathbf{R^{11}}$, -C(=O)-$\mathbf{R^{11}}$, -C(=O)-O-$\mathbf{R^{11}}$, -O-$\mathbf{R^{11}}$, -S-$\mathbf{R^{11}}$, -SO-$\mathbf{R^{11}}$, -SO_2-$\mathbf{R^{11}}$, -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -(C_{1-6})alkylene-C(=O)-$\mathbf{R^{11}}$, -(C_{1-6})alkylene-C(=O)-O-$\mathbf{R^{11}}$, -(C_{1-6})alkylene-O-$\mathbf{R^{11}}$, –(C_{1-6})alkylene-S-$\mathbf{R^{11}}$, -(C_{1-6})alkylene-SO-$\mathbf{R^{11}}$ or -(C_{1-6})alkylene-SO_2-$\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -SO_2(C_{1-6})alkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N((C_{1-4})alkyl)$_2$, -C(=O)-aryl, --C(=O)-**Het**, NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

c) -N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –O-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –SO_2-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene–O-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, or -(C_{1-6})alkylene-SO_2-N($\mathbf{R^9}$)$\mathbf{R^{10}}$ wherein

$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -SO_2-$\mathbf{R^{11}}$, -C(=O)-$\mathbf{R^{11}}$, -C(=O)O$\mathbf{R^{11}}$ and -C(=O)N($\mathbf{R^9}$)$\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above; or

or $\mathbf{R^5}$ and $\mathbf{R^6}$, together with the C to which they are attached, may be linked to form a 5- or 6-membered carbocycle or a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an

oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2;

wherein the carbocycle or heterocycle is optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})alkyl)_2$.

R^5-B: In one embodiment, R^5 is H, halo, (C_{1-6})alkyl, (C_{1-6})haloalkyl or -O(C_{1-6})alkyl.

R^5-C: In one embodiment, R^5 is H, halo, (C_{1-4})alkyl or (C_{1-4})haloalkyl.

R^5-D: In one embodiment, R^5 is H, halo or (C_{1-4})alkyl.

R^5-E: In one embodiment, R^5 is F or H.

R^5-F: In one embodiment, R^5 is H, F or CH_3.

R^5-G: In one embodiment, R^5 is H.

Any and each individual definition of R^5 as set out herein may be combined with any and each individual definition of the **Core**, **c**, R^2, R^3, R^4, R^6, R^7 and R^8 as set out herein.

R^6:

R^6-A: In one embodiment, R^6 is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) -C(=O)-R^{11}, -C(=O)-O-R^{11}, -O-R^{11}, -S-R^{11}, -SO-R^{11}, -SO_2-R^{11}, -(C_{1-6})alkylene-R^{11}, -(C_{1-6})alkylene-C(=O)-R^{11}, -(C_{1-6})alkylene-C(=O)-O-R^{11}, -(C_{1-6})alkylene-O-R^{11}, –(C_{1-6})alkylene-S-R^{11}, -(C_{1-6})alkylene-SO-R^{11} or -(C_{1-6})alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

c) -N(R^9)R^{10}, –C(=O)-N(R^9)R^{10}, –O-C(=O)-N(R^9)R^{10}, –SO_2-N(R^9)R^{10}, -(C_{1-6})alkylene-N(R^9)R^{10}, -(C_{1-6})alkylene-C(=O)-N(R^9)R^{10}, -(C_{1-6})alkylene–O-C(=O)-N(R^9)R^{10}, or -(C_{1-6})alkylene-SO_2-N(R^9)R^{10} wherein

R^9 is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -SO_2-$\mathbf{R^{11}}$, -C(=O)-$\mathbf{R^{11}}$, -C(=O)O$\mathbf{R^{11}}$ and -C(=O)N($\mathbf{R^9}$)$\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -SO_2(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

$\mathbf{R^6}$ may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when $\mathbf{R^2}$ is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl; or

$\mathbf{R^5}$ and $\mathbf{R^6}$, together with the C to which they are attached or $\mathbf{R^6}$ and $\mathbf{R^7}$, together with the C to which they are attached may be linked to form a 5- or 6-membered carbocycle or a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2;

wherein the carbocycle or heterocycle is optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$.

R^6-B: In one embodiment, $\mathbf{R^6}$ is selected from:

a) (C_{2-6})alkenyl, aryl and **Het**; and

b) -O-(C_{1-6})alkyl; or

$\mathbf{R^6}$ may also be halo when at least one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when $\mathbf{R^2}$ is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

R^6-C: In one embodiment, $\mathbf{R^6}$ is H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl, when at least

one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

R^6-D: In another embodiment, R^6 is $CH=CH_2$, phenyl, OCH_3; or CH_3, CH_2CH_3, H, F, Cl or Br when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

R^6-E: In another embodiment, R^6 is $CH=CH_2$, phenyl, or OCH_3; or H, Br,CH_3 or CH_2CH_3 when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

R^6-F: In another embodiment, R^6 is H when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

R^6-G: In another embodiment, R^6 is C≡CH, $CH=CH_2$, phenyl or OCH_3; or H, Br when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

Any and each individual definition of R^6 as set out herein may be combined with any and each individual definition of the **Core**, **c**, R^2, R^3, R^4, R^5, R^7 and R^8 as set out herein.

R^7:

R^7-A: In one embodiment, R^7 is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) -C(=O)-R^{11}, -C(=O)-O-R^{11}, -O-R^{11}, -S-R^{11}, -SO-R^{11}, -SO_2-R^{11}, -(C_{1-6})alkylene-R^{11}, -(C_{1-6})alkylene-C(=O)-R^{11}, -(C_{1-6})alkylene-C(=O)-O-R^{11}, -(C_{1-6})alkylene-O-R^{11}, –(C_{1-6})alkylene-S-R^{11}, -(C_{1-6})alkylene-SO-R^{11} or -(C_{1-6})alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**; and

c) -N(R^9)R^{10}, –C(=O)-N(R^9)R^{10}, –O-C(=O)-N(R^9)R^{10}, –SO_2-N(R^9)R^{10},

-(C_{1-6})alkylene-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene–O-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, or -(C_{1-6})alkylene-SO_2-N($\mathbf{R^9}$)$\mathbf{R^{10}}$ wherein

$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -SO_2-$\mathbf{R^{11}}$, -C(=O)-$\mathbf{R^{11}}$, -C(=O)O$\mathbf{R^{11}}$ and -C(=O)N($\mathbf{R^9}$)$\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -SO_2(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

$\mathbf{R^7}$ may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when $\mathbf{R^6}$ is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when $\mathbf{R^2}$ is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl; or

$\mathbf{R^6}$ and $\mathbf{R^7}$, together with the C to which they are attached, or $\mathbf{R^7}$ and $\mathbf{R^8}$, together with the C to which they are attached; may be linked to form a 5- or 6-membered carbocycle or a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2;

wherein the carbocycle or heterocycle is optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$.

$\mathbf{R^7}$-**B**: In one embodiment, $\mathbf{R^7}$ is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -(C_{1-6})alkylene-O-$\mathbf{R^{11}}$,
wherein $\mathbf{R^{11}}$ is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**; and

c) -$N(\mathbf{R^9})\mathbf{R^{10}}$, –C(=O)-$N(\mathbf{R^9})\mathbf{R^{10}}$, -$(C_{1-6})$alkylene-$N(\mathbf{R^9})\mathbf{R^{10}}$, -$(C_{1-6})$alkylene-C(=O)-$N(\mathbf{R^9})\mathbf{R^{10}}$, wherein
$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and
$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -SO_2-$\mathbf{R^{11}}$, -C(=O)-$\mathbf{R^{11}}$, -C(=O)O$\mathbf{R^{11}}$ and -C(=O)$N(\mathbf{R^9})\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -$SO_2(C_{1-6})$alkyl, -NH_2, -NH(C_{1-6})alkyl and -N$((C_{1-6})\text{alkyl})_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; or

$\mathbf{R^7}$ may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when $\mathbf{R^6}$ is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when $\mathbf{R^2}$ is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

$\mathbf{R^7}$-C: In one embodiment, $\mathbf{R^7}$ is selected from:

a) (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) -(C_{1-6})alkylene-$\mathbf{R^{11}}$,
wherein $\mathbf{R^{11}}$ is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**; and

c) -$N(\mathbf{R^9})\mathbf{R^{10}}$, –C(=O)-$N(\mathbf{R^9})\mathbf{R^{10}}$, wherein
$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -SO_2-$\mathbf{R^{11}}$, -C(=O)-$\mathbf{R^{11}}$, -C(=O)O$\mathbf{R^{11}}$ and -C(=O)N($\mathbf{R^9}$)$\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -SO_2(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH;

$\mathbf{R^7}$ may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when $\mathbf{R^6}$ is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when $\mathbf{R^2}$ is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

$\mathbf{R^7}$-D: In one embodiment, $\mathbf{R^7}$ is selected from:

a) aryl or **Het**; and

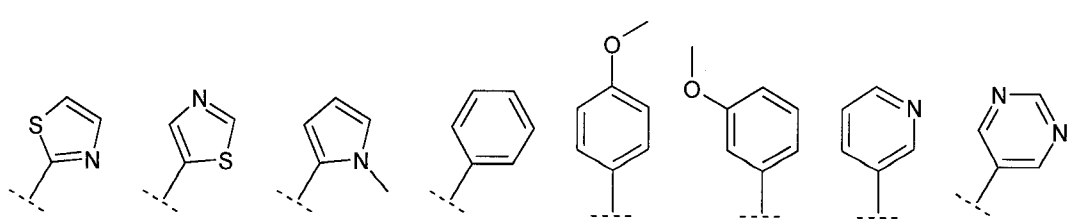
b) -(C_{1-6})alkylene-$\mathbf{R^{11}}$, wherein $\mathbf{R^{11}}$ is in each instance independently selected from aryl and **Het**;

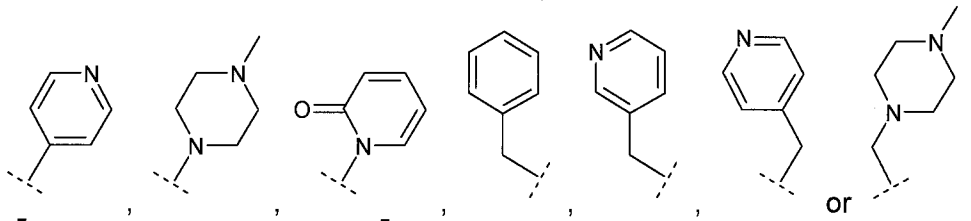
wherein said aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{1-6})haloalkyl, -OH, -O(C_{1-6})alkyl, -O (C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -SO_2(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$; and

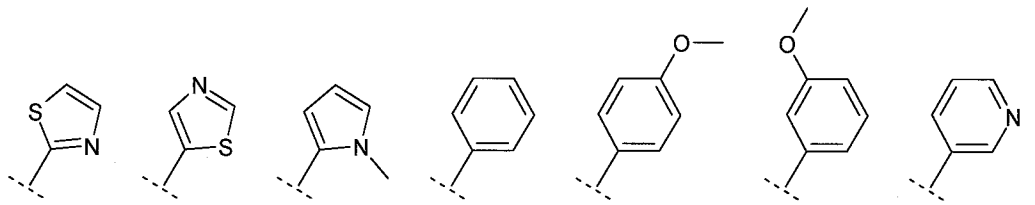
ii) (C_{1-6})alkyl.

$\mathbf{R^7}$-E: In one embodiment, $\mathbf{R^7}$ is CH_2OH, CN, OCH_3, $CH=CH_2$, cyclopropyl, NH_2, NO_2, $CONH_2$, $NHC(=O)CH_3$,





R^7-F: In one embodiment, **R^7** is CH_2OH, CN, OCH_3, $CH=CH_2$, cyclopropyl, NH_2, NO_2, $CONH_2$, $NHC(=O)CH_3$,



H, when at least one of **R^5** or **R^8** is other than H or when **R^6** is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when **R^2** is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

R^7-G: In one embodiment, **R^7** is H, when at least one of **R^5** or **R^8** is other than H or when **R^6** is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when **R^2** is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

Any and each individual definition of **R^7** as set out herein may be combined with any and each individual definition of the **Core**, **c**, **R^2**, **R^3**, **R^4**, **R^5**, **R^6** and **R^8** as set out herein.

R^8:

R^8-A: In another embodiment, **R^8** is selected from:

a) halo, nitro or cyano;

b) **R^{11}**, -C(=O)-**R^{11}**, -C(=O)-O-**R^{11}**, -O-**R^{11}**, -S-**R^{11}**, -SO-**R^{11}**, -SO_2-**R^{11}**, -(C_{1-6})alkylene-**R^{11}**, -(C_{1-6})alkylene-C(=O)-**R^{11}**, -(C_{1-6})alkylene-C(=O)-O-**R^{11}**, -(C_{1-6})alkylene-O-**R^{11}**, –(C_{1-6})alkylene-S-**R^{11}**, -(C_{1-6})alkylene-SO-**R^{11}** or -(C_{1-6})alkylene-SO_2-**R^{11}**;

wherein $\mathbf{R^{11}}$ is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O (C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -$SO_2(C_{1-6})$alkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N$((C_{1-4})\text{alkyl})_2$, -C(=O)-aryl, --C(=O)-**Het**, NH_2, -NH(C_{1-6})alkyl and -N$((C_{1-6})\text{alkyl})_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

c) -N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –O-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, –SO_2-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, -(C_{1-6})alkylene–O-C(=O)-N($\mathbf{R^9}$)$\mathbf{R^{10}}$, or -(C_{1-6})alkylene-SO_2-N($\mathbf{R^9}$)$\mathbf{R^{10}}$

wherein

$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, -(C_{1-6})alkylene-$\mathbf{R^{11}}$, -SO_2-$\mathbf{R^{11}}$, -C(=O)-$\mathbf{R^{11}}$, -C(=O)O$\mathbf{R^{11}}$ and -C(=O)N($\mathbf{R^9}$)$\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above;

or $\mathbf{R^7}$ and $\mathbf{R^8}$, together with the C to which they are attached; may be linked to form a 5- or 6-membered carbocycle or a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2;

wherein the carbocycle or heterocycle is optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl,

(C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})alkyl)_2$.

R^8-B: In another embodiment, R^8 is selected from:

a) halo;

b) R^{11}, -O-R^{11}, or -(C_{1-6})alkylene-R^{11}

wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, aryl and **Het**;

and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{1-6})haloalkyl, -OH, -O(C_{1-6})alkyl, -O (C_{1-6})haloalkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N$((C_{1-4})alkyl)_2$, -C(=O)-aryl, --C(=O)-**Het**, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})alkyl)_2$;

ii) (C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

c) -N(R^9)R^{10}, –C(=O)-N(R^9)R^{10}, –O-C(=O)-N(R^9)R^{10}, $–SO_2$-N(R^9)R^{10}, -(C_{1-6})alkylene-N(R^9)R^{10}, -(C_{1-6})alkylene-C(=O)-N(R^9)R^{10}, -(C_{1-6})alkylene–O-C(=O)-N(R^9)R^{10}, or -(C_{1-6})alkylene-SO_2-N(R^9)R^{10}

wherein

R^9 is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

R^{10} is in each instance independently selected from R^{11}, -(C_{1-6})alkylene-R^{11}, $-SO_2$-R^{11}, -C(=O)-R^{11}, -C(=O)OR^{11} and -C(=O)N(R^9)R^{11}; wherein R^{11} and R^9 are as defined above.

R^8-C: In another embodiment, R^8 is selected from:

a) halo; and

b) H, (C_{1-6})alkyl, (C_{1-6})haloalkyl, -O-(C_{1-6})haloalkyl, aryl and **Het**, -(C_{1-6})alkylene-aryl, -(C_{1-6})alkylene-**Het**;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, -O(C_{1-6})alkyl, -O (C_{1-6})haloalkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N$((C_{1-4})alkyl)_2$, -C(=O)-aryl,

--C(=O)-**Het**; and

ii) (C_{1-6})alkyl.

R^8-D: In another embodiment, **R^8** is selected from:

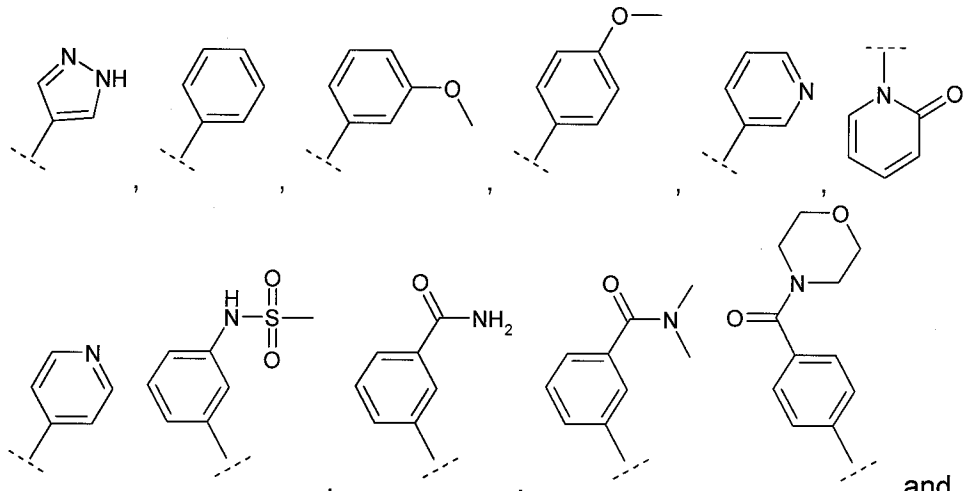
a) F, Cl, Br; and

b) H, (C_{1-3})alkyl, , -O-(C_{1-3})haloalkyl, phenyl and **Het**, -(C_{1-3})alkylene-phenyl, -(C_{1-3})alkylene-**Het**; wherein each of the aryl and **Het** is optionally substituted with 1 to 2 substituents each independently selected from:

i) oxo, thioxo, -O(C_{1-6})alkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N$((C_{1-4})alkyl)_2$, -C(=O)-aryl, --C(=O)-**Het**; and

ii) (C_{1-6})alkyl.

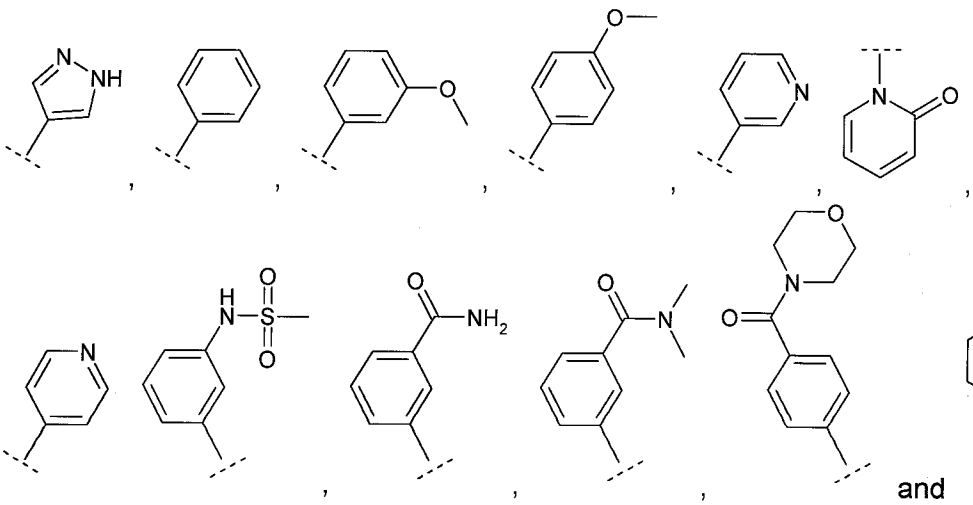
R^8-E: In another embodiment, **R^8** is selected from: H, Br, F, CH_3, CH_2CH_3, OCF_3



and .

R^8-F: In another embodiment, **R^8** is H, Br, F, CH_3, CH_2CH_3 or OCF_3.

R^8-G: In another embodiment, **R^8** is selected from:



and .

Any and each individual definition of R^8 as set out herein may be combined with any and each individual definition of the **Core**, **c**, R^2, R^3, R^4, R^5, R^6 and R^7 as set out herein.

Examples of preferred subgeneric embodiments of the present invention are set forth in the following table, wherein each substituent group of each embodiment is defined according to the definitions set forth above:

Embodiment	Core	R^2	R^3	R^4	R^5	R^6	R^7	R^8
E-1	Core-A	R^2-I	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-D
E-2	Core-A	R^2-H	R^3-I	R^4-I	R^5-E	R^6-E	R^7-D	R^8-B
E-3	Core-A	R^2-E	R^3-I	R^4-J	R^5-F	R^6-F	R^7-F	R^8-G
E-4	Core-A	R^2-I	R^3-J	R^4-K	R^5-G	R^6-G	R^7-F	R^8-E
E-5	Core-A	R^2-H	R^3-B	R^4-L	R^5-D	R^6-A	R^7-D	R^8-F
E-6	Core-A	R^2-E	R^3-C	R^4-H	R^5-D	R^6-G	R^7-D	R^8-G
E-7	Core-A	R^2-H	R^3-I	R^4-L	R^5-F	R^6-F	R^7-F	R^8-E
E-8	Core-A	R^2-A	R^3-A	R^4-K	R^5-E	R^6-G	R^7-B	R^8-A
E-9	Core-A	R^2-B	R^3-D	R^4-H	R^5-F	R^6-D	R^7-C	R^8-C
E-10	Core-A	R^2-C	R^3-E	R^4-L	R^5-G	R^6-D	R^7-A	R^8-C
E-11	Core-A	R^2-D	R^3-A	R^4-B	R^5-A	R^6-E	R^7-D	R^8-D
E-12	Core-A	R^2-B	R^3-F	R^4-K	R^5-F	R^6-D	R^7-F	R^8-G
E-13	Core-A	R^2-C	R^3-E	R^4-L	R^5-G	R^6-E	R^7-G	R^8-E
E-14	Core-A	R^2-D	R^3-B	R^4-J	R^5-C	R^6-F	R^7-B	R^8-G
E-15	Core-A	R^2-E	R^3-G	R^4-A	R^5-E	R^6-G	R^7-G	R^8-D
E-16	Core-A	R^2-G	R^3-A	R^4-B	R^5-A	R^6-D	R^7-G	R^8-E
E-17	Core-A	R^2-F	R^3-H	R^4-E	R^5-D	R^6-E	R^7-A	R^8-F
E-18	Core-A	R^2-H	R^3-C	R^4-D	R^5-B	R^6-F	R^7-G	R^8-B
E-19	Core-A	R^2-I	R^3-D	R^4-F	R^5-D	R^6-A	R^7-C	R^8-C
E-20	Core-A	R^2-I	R^3-I	R^4-C	R^5-E	R^6-B	R^7-G	R^8-A
E-21	Core-A	R^2-I	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-G
E-22	Core-A	R^2-H	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-G
E-23	Core-A	R^2-E	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-G
E-24	Core-B	R^2-I	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-D

Embodiment	Core	R^2	R^3	R^4	R^5	R^6	R^7	R^8
E-25	Core-B	R^2-H	R^3-I	R^4-I	R^5-E	R^6-E	R^7-D	R^8-B
E-26	Core-B	R^2-E	R^3-I	R^4-J	R^5-F	R^6-F	R^7-F	R^8-G
E-27	Core-B	R^2-I	R^3-J	R^4-K	R^5-G	R^6-G	R^7-F	R^8-E
E-28	Core-B	R^2-I	R^3-I	R^4-K	R^5-G	R^6-G	R^7-F	R^8-E
E-29	Core-B	R^2-I	R^3-I	R^4-K	R^5-G	R^6-G	R^7-G	R^8-E
E-30	Core-B	R^2-H	R^3-B	R^4-L	R^5-D	R^6-A	R^7-D	R^8-F
E-31	Core-B	R^2-E	R^3-C	R^4-H	R^5-D	R^6-G	R^7-D	R^8-G
E-32	Core-B	R^2-H	R^3-I	R^4-L	R^5-F	R^6-F	R^7-F	R^8-E
E-33	Core-B	R^2-I	R^3-I	R^4-J	R^5-F	R^6-B	R^7-E	R^8-B
E-34	Core-B	R^2-E	R^3-B	R^4-K	R^5-G	R^6-D	R^7-E	R^8-D
E-35	Core-B	R^2-E	R^3-C	R^4-J	R^5-	R^6-E	R^7-D	R^8-E
E-36	Core-B	R^2-H	R^3-E	R^4-J	R^5-C	R^6-C	R^7-F	R^8-D
E-37	Core-B	R^2-H	R^3-F	R^4-I	R^5-D	R^6-F	R^7-F	R^8-B
E-38	Core-B	R^2-A	R^3-A	R^4-K	R^5-E	R^6-G	R^7-B	R^8-A
E-39	Core-B	R^2-B	R^3-D	R^4-H	R^5-F	R^6-D	R^7-C	R^8-C
E-40	Core-B	R^2-C	R^3-E	R^4-L	R^5-G	R^6-D	R^7-A	R^8-C
E-41	Core-B	R^2-D	R^3-A	R^4-B	R^5-A	R^6-E	R^7-D	R^8-D
E-42	Core-B	R^2-E	R^3-J	R^4-C	R^5-B	R^6-A	R^7-F	R^8-B
E-43	Core-B	R^2-F	R^3-I	R^4-D	R^5-D	R^6-B	R^7-E	R^8-B
E-44	Core-B	R^2-G	R^3-C	R^4-E	R^5-E	R^6-C	R^7-D	R^8-C
E-45	Core-B	R^2-A	R^3-D	R^4-A	R^5-F	R^6-C	R^7-E	R^8-D
E-46	Core-B	R^2-B	R^3-F	R^4-K	R^5-F	R^6-D	R^7-F	R^8-G
E-47	Core-B	R^2-C	R^3-E	R^4-L	R^5-G	R^6-E	R^7-G	R^8-E
E-48	Core-B	R^2-D	R^3-B	R^4-J	R^5-C	R^6-F	R^7-B	R^8-G
E-49	Core-B	R^2-E	R^3-G	R^4-A	R^5-E	R^6-G	R^7-G	R^8-D
E-50	Core-B	R^2-G	R^3-A	R^4-B	R^5-A	R^6-D	R^7-G	R^8-E
E-51	Core-B	R^2-F	R^3-H	R^4-E	R^5-D	R^6-E	R^7-A	R^8-F
E-52	Core-B	R^2-H	R^3-C	R^4-D	R^5-B	R^6-F	R^7-G	R^8-B
E-53	Core-B	R^2-I	R^3-D	R^4-F	R^5-D	R^6-A	R^7-C	R^8-C
E-54	Core-B	R^2-I	R^3-I	R^4-C	R^5-E	R^6-B	R^7-G	R^8-A
E-55	Core-B	R^2-I	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-G
E-56	Core-B	R^2-H	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-G

Embodiment	Core	R^2	R^3	R^4	R^5	R^6	R^7	R^8
E-57	Core-B	R^2-E	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-G
E-58	Core-C	R^2-I	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-D
E-59	Core-C	R^2-H	R^3-I	R^4-I	R^5-E	R^6-E	R^7-D	R^8-B
E-60	Core-C	R^2-E	R^3-I	R^4-J	R^5-F	R^6-F	R^7-F	R^8-G
E-61	Core-C	R^2-H	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-G
E-62	Core-C	R^2-E	R^3-I	R^4-H	R^5-D	R^6-D	R^7-E	R^8-G

Examples of most preferred compounds according to this invention are each single compound listed in the following Tables 1 to 4.

In general, all tautomeric and isomeric forms and mixtures thereof, for example, individual tautomers, geometric isomers, stereoisomers, atropisomers, enantiomers, diastereomers, racemates, racemic or non-racemic mixtures of stereoisomers, mixtures of diastereomers, or mixtures of any of the foregoing forms of a chemical structure or compound is intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure.

It is well-known in the art that the biological and pharmacological activity of a compound is sensitive to the stereochemistry of the compound. Thus, for example, enantiomers often exhibit strikingly different biological activity including differences in pharmacokinetic properties, including metabolism, protein binding, and the like, and pharmacological properties, including the type of activity displayed, the degree of activity, toxicity, and the like. Thus, one skilled in the art will appreciate that one enantiomer may be more active or may exhibit beneficial effects when enriched relative to the other enantiomer or when separated from the other enantiomer. Additionally, one skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of the present invention from this disclosure and the knowledge in the art.

Preparation of pure stereoisomers, e.g. enantiomers and diastereomers, or mixtures of desired enantiomeric excess (ee) or enantiomeric purity, are accomplished by one or more of the many methods of (a) separation or resolution of enantiomers, or (b) enantioselective synthesis known to those of skill in the art, or a combination thereof. These resolution methods generally rely on chiral recognition and include, for

example, chromatography using chiral stationary phases, enantioselective host-guest complexation, resolution or synthesis using chiral auxiliaries, enantioselective synthesis, enzymatic and nonenzymatic kinetic resolution, or spontaneous enantioselective crystallization. Such methods are disclosed generally in Chiral Separation Techniques: A Practical Approach (2nd Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, Chiral Chromatography, John Wiley & Sons, 1999; and Satinder Ahuja, Chiral Separations by Chromatography, Am. Chem. Soc., 2000, herein incorporated by reference. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, for example, GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, for example, CD, ORD, X-ray crystallography, or NMR.

Pharmaceutical composition

Compounds of the present invention may be administered to a mammal in need of treatment for HIV infection as a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the invention or a pharmaceutically acceptable salt or ester thereof; and one or more conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The specific formulation of the composition is determined by the solubility and chemical nature of the compound, the chosen route of administration and standard pharmaceutical practice. The pharmaceutical composition according to the present invention may be administered orally or systemically.

When one enantiomer of a chiral active ingredient has a different biological activity than the other, it is contemplated that the pharmaceutical composition according to the invention may comprise a racemic mixture of the active ingredient, a mixture enriched in one enantiomer of the active ingredient or a pure enantiomer of the active ingredient. The mixture enriched in one enantiomer of the active ingredient is contemplated to contain from more than 50% to about 100% of one enantiomer of the active ingredient and from about 0% to less than 50% of the other enantiomer of the active ingredient. Preferably, when the composition comprises a mixture enriched in one enantiomer of the active ingredient or a pure enantiomer of the active ingredient, the composition comprises from more than 50% to about 100% of, or only, the more physiologically active enantiomer and/or the less toxic enantiomer. It is well known that one enantiomer of an active ingredient may be the more

physiologically active for one therapeutic indication while the other enantiomer of the active ingredient may be the more physiologically active for a different therapeutic indication; therefore the preferred enantiomeric makeup of the pharmaceutical composition may differ for use of the composition in treating different therapeutic indications.

For oral administration, the compound, or a pharmaceutically acceptable salt or ester thereof, can be formulated in any orally acceptable dosage form including but not limited to aqueous suspensions and solutions, capsules or tablets. For systemic administration, including but not limited to administration by subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques, it is preferred to use a solution of the compound, or a pharmaceutically acceptable salt or ester thereof, in a pharmaceutically acceptable sterile aqueous vehicle.

Pharmaceutically acceptable carriers, adjuvants, vehicles, excipients and additives as well as methods of formulating pharmaceutical compositions for various modes of administration are well-known to those of skill in the art and are described in pharmaceutical texts such as Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins, 2005; and L.V. Allen, N.G. Popovish and H.C. Ansel, Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th ed., Lippincott Williams & Wilkins, 2004, herein incorporated by reference.

The dosage administered will vary depending upon known factors, including but not limited to the activity and pharmacodynamic characteristics of the specific compound employed and its mode, time and route of administration; the age, diet, gender, body weight and general health status of the recipient; the nature and extent of the symptoms; the severity and course of the infection; the kind of concurrent treatment; the frequency of treatment; the effect desired; and the judgment of the treating physician. In general, the compound is most desirably administered at a dosage level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

A daily dosage of active ingredient can be expected to be about 0.001 to about 100 milligrams per kilogram of body weight, with the preferred dose being about 0.01 to

about 50 mg/kg. Typically, the pharmaceutical composition of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (*w/w*). Preferably, such preparations contain from about 20% to about 80% active compound.

Therefore, according to one embodiment, the pharmaceutical composition according to the invention comprises a racemic mixture of the compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

An alternative embodiment provides a pharmaceutical composition comprising a mixture enriched in one enantiomer of the compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

A further embodiment provides a pharmaceutical composition comprising a pure enantiomer of the compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

Combination therapy

Combination therapy is contemplated wherein a compound according to the invention, or a pharmaceutically acceptable salt or ester thereof, is co-administered with at least one additional antiviral agent. The additional agents may be combined with compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered, concurrently or sequentially, as part of a multiple dosage form.

When the pharmaceutical composition of this invention comprises a combination of a compound according to the invention, or a pharmaceutically acceptable salt or ester thereof, and one or more additional antiviral agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen. In the case of a synergistic interaction

between the compound of the invention and the additional antiviral agent or agents, the dosage of any or all of the active agents in the combination may be reduced compared to the dosage normally administered in a monotherapy regimen.

Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of a virus in a mammal, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal. Such agents can be selected from:

- NRTIs (nucleoside or nucleotide reverse transcriptase inhibitors) including but not limited to zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), emtricitabine, abacavir succinate, elvucitabine, adefovir dipivoxil, lobucavir (BMS-180194) lodenosine (FddA) and tenofovir including tenofovir disoproxil and tenofovir disoproxil fumarate salt, COMBIVIR™ (contains 3TC and AZT), TRIZIVIR™ (contains abacavir, 3TC and AZT), TRUVADA™ (contains tenofovir and emtricitabine), EPZICOM™ (contains abacavir and 3TC);
- NNRTIs (non-nucleoside reverse transcriptase inhibitors) including but not limited to nevirapine, delaviradine, efavirenz, etravirine and rilpivirine;
- protease inhibitors including but not limited to ritonavir, tipranavir, saquinavir, nelfinavir, indinavir, amprenavir, fosamprenavir, atazanavir, lopinavir, darunavir (TMC-114), lasinavir and brecanavir (VX-385);
- entry inhibitors including but not limited to
    - CCR5 antagonists (including but not limited to maraviroc, vicriviroc, INCB9471 and TAK-652),
    - CXCR4 antagonists (including but not limited to AMD-11070),
    - fusion inhibitors (including but not limited to enfuvirtide (T-20), TR1-1144 and TR1-999) and
    - others (including but not limited to BMS-488043);
- integrase inhibitors (including but not limited to raltegravir (MK-0518), BMS-707035 and elvitegravir (GS 9137));
- TAT inhibitors;
- maturation inhibitors (including but not limited to berivimat (PA-457));
- immunomodulating agents (including but not limited to levamisole); and
- other antiviral agents including hydroxyurea, ribavirin, IL-2, IL-12 and

pensafuside.

Furthermore, a compound according to the invention can be used with at least one other compound according to the invention or with one or more antifungal or antibacterial agents (including but not limited to fluconazole).

Therefore, according to one embodiment, the pharmaceutical composition of this invention additionally comprises one or more antiviral agents.

A further embodiment provides the pharmaceutical composition of this invention wherein the one or more antiviral agent comprises at least one NNRTI.

According to another embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one NRTI.

According to yet another embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one protease inhibitor.

According to still another embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one entry inhibitor.

According to a further embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one integrase inhibitor.

A compound according to the present invention may also be used as a laboratory reagent or a research reagent. For example, a compound of the present invention may be used as positive control to validate assays, including but not limited to surrogate cell-based assays and *in vitro* or *in vivo* viral replication assays.

Furthermore, a compound according to the present invention may be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials (e.g. blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection apparatuses and materials).

Derivatives comprising a detectable label

Another aspect of the invention provides a derivative of a compound of formula (I), the derivative comprising a detectable label. Such a label allows recognition either directly or indirectly of the derivative such that it can be detected, measured or quantified. The detectable label may itself be detectable, measurable or quantifiable, or it may interact with one or more other moities which themselves comprise one or more detectable labels, so that the interaction therebetween allows the derivative to be detected, measured or quantified.

Such derivatives may be used as probes to study HIV replication, including but not limited to study of the mechanism of action of viral and host proteins involved in HIV replication, study of conformational changes undergone by such viral and host proteins under various conditions and study of interactions with entities which bind to or otherwise interact with these viral and host proteins. Derivatives according to this aspect of the invention may be used in assays to identify compounds which interact with viral and host proteins, the assays including but not limited to displacement assays which measure the extent to which the derivative is displaced from interacting with the viral and host proteins. A preferred use of derivatives according to this aspect of the invention is in assays to identify HIV integrase inhibitors. Such derivatives may also be used to form covalent or non-covalent interactions with the viral and host proteins or to identify residues of the viral and host proteins which interact with the compounds of the invention.

Detectable labels contemplated for use with derivatives of the compounds of the invention include, but are not limited to, fluorescent labels, chemiluminescent labels, chromophores, antibodies, enzymatic markers, radioactive isotopes, affinity tags and photoreactive groups.

A fluorescent label is a label which fluoresces, emitting light of one wavelength upon absorption of light of a different wavelength. Fluorescent labels include but are not limited to fluorescein; Texas Red; aminomethylcoumarin; rhodamine dyes, including but not limited to tetramethylrhodamine (TAMRA); Alexa dyes including but not limited to Alexa Fluor® 555; cyanine dyes including but not limited to Cy3; europium or lanthanide series based fluorescent molecules; and the like.

A chemiluminescent label is a label which can undergo a chemical reaction which produces light. Chemiluminescent labels include but are not limited to luminol, luciferin, lucigenin, and the like.

A chromophore is a label which selectively absorbs certain wavelengths of visible light while transmitting or reflecting others, thereby causing the compounds which contain the chromophore to appear colored. Chromophores include but are not limited to natural and synthetic dyes.

An antibody is a protein produced by a mammalian immune system in response to a specific antigen, which binds specifically to that antigen. Antibodies contemplated for use as detectable labels according to the invention include but are not limited to antibodies against the following: polyhistidine tags, glutathione-S-transferase (GST), hemagglutinin (HA), FLAG® epitope tags, Myc tag, maltose binding protein (MBP), green fluorescent protein (GFP) and the like.

An enzymatic marker is an enzyme whose presence may be detected by means of an assay specific to the catalytic activity of the enzyme. Enzymatic markers contemplated for use as detectable labels according to the invention include but are not limited to luciferase, horseradish peroxidase (HRP), β-galactosidase and the like.

A radioactive isotope is an isotope of an atom which produces radiation upon radioactive decay. Radioactive isotopes include but are not limited to ^{14}C, ^{3}H, ^{31}P, ^{121}I, ^{125}I and the like.

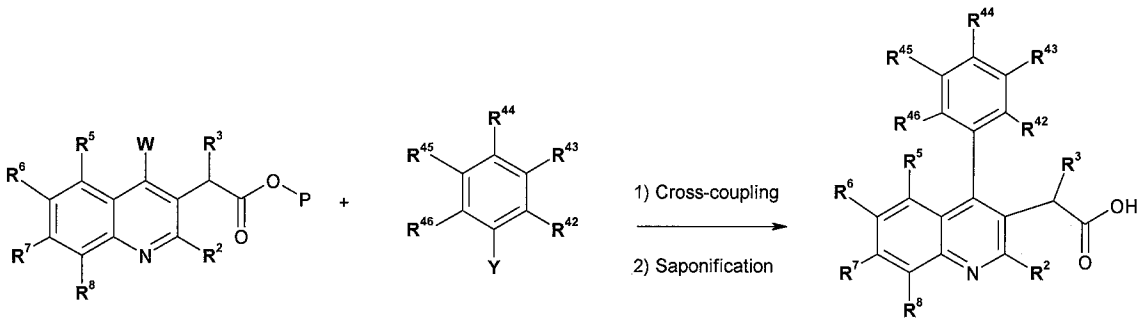
An affinity tag is a label which has a strong affinity for another moiety, designated herein as a binding partner. Such an affinity tag can be used to form a complex with the binding partner so that the complex may be selectively detected or separated from a mixture. Affinity tags include but are not limited to biotin or a derivative thereof, a histidine polypeptide, a polyarginine, an amylose sugar moiety or a defined epitope recognizable by a specific antibody; suitable epitopes include but are not limited to glutathione-S-transferase (GST), hemagglutinin (HA), FLAG® epitope tags, Myc tag, maltose binding protein (MBP), green fluorescent protein (GFP) and the like.

Furthermore, compounds of the invention used as probes may be labelled with a photoreactive group which is transformed, upon activation by light, from an inert group to a reactive species, such as a free radical. Such a group may be used to activate the derivative so that it can form a covalent bond with one or more residues of a viral or host protein. Photoreactive groups include but are not limited to photoaffinity labels such as benzophenone and azide groups.

Methodology and Synthesis

The synthesis of compounds of formula (I) according to this invention is conveniently accomplished following the general procedure outlined in the schemes below wherein R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein. Further instruction is provided to one skilled in the art by the specific examples set out herein below.

Scheme 1: Assembly of inhibitors



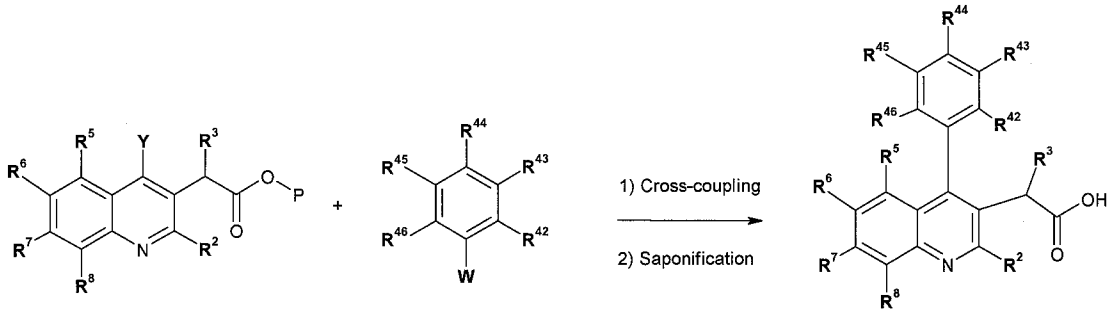
Intermediate I Intermediate II

wherein R^{42}, R^{43}, R^{44}, R^{45} and R^{46} may either be substituents on the phenyl moiety or (R^{42} and R^{43}), (R^{43} and R^{44}), (R^{44} and R^{45}) or (R^{45} and R^{46}) may be linked so to as to form a carbocycle or heterocycle, **W** is iodo, bromo, chloro or OTf, **Y** is $B(OH)_2$ or boronate esters such as $B(OCH_3)_2$ and $B(OC(CH_3)_2C(CH_3)_2O)$, iodo, SnR_3 wherein R is (C_{1-6})alkyl, ZnX wherein X is halo, and P is a protecting group, such as commonly used protecting groups for carboxylic acids, including, but not limited to a methyl or ethyl ester.

Several coupling methods between the intermediate (**I**) (i.e. quinoline scaffold) and the intermediate **II** (i.e. R^4 substituent) can be contemplated by those skilled in the art. For examples, but not limited to, Suzuki cross-coupling between the boronic acid or boronate ester derivative of intermediate **II** and the halo or triflate derivative of intermediate **I**, copper catalyzed Ullmann cross-coupling between the iodo

derivatives of intermediates **I** and **II**, Negishi cross-coupling between the arylzinc reagent of the intermediate **II** and the iodo or triflate derivative of intermediate **I**, and Stille coupling between the arylltin reagent of **II** and the bromo or iodo derivative of intermediate **I** as shown above can lead, after saponification, to the compounds of formula (I).

Alternatively, the same cross-coupling methods can be used by interchanging the coupling partners as shown below. For examples, Suzuki, Negishi, and Stille type cross-coupling between boronic acid or boronate ester derivative, the arylzinc reagent or the arylltin reagent of quinoline intermediate **III** and the required iodo, bromo, chloro or triflate derivative of intermediate **IV** can also lead, after saponification, to the compounds of the invention of formula (I).

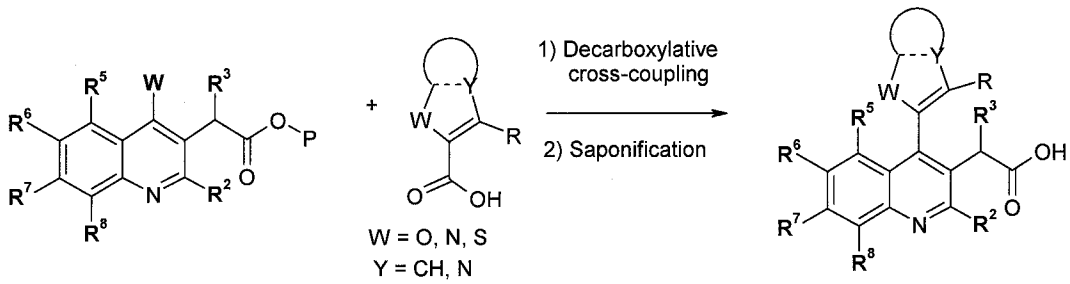


Intermediate III Intermediate IV

wherein R^{42}, R^{43}, R^{44}, R^{45} and, R^{46} and **P** are as defined above and **W** is iodo, bromo, chloro or OTf, **Y** is $B(OH)_2$ or boronate esters such as $B(OCH_3)_2$ and $B(OC(CH_3)_2C(CH_3)_2O)$, SnR_3 wherein R is (C_{1-6})alkyl, and ZnX wherein X is halo.

Furthermore, downstream modifications to the product can be contemplated, such as conversion of an aniline-type amine to a chloro or bromo substituent via Sandmeyer reaction or alkylation, or dehalogenation via reduction.

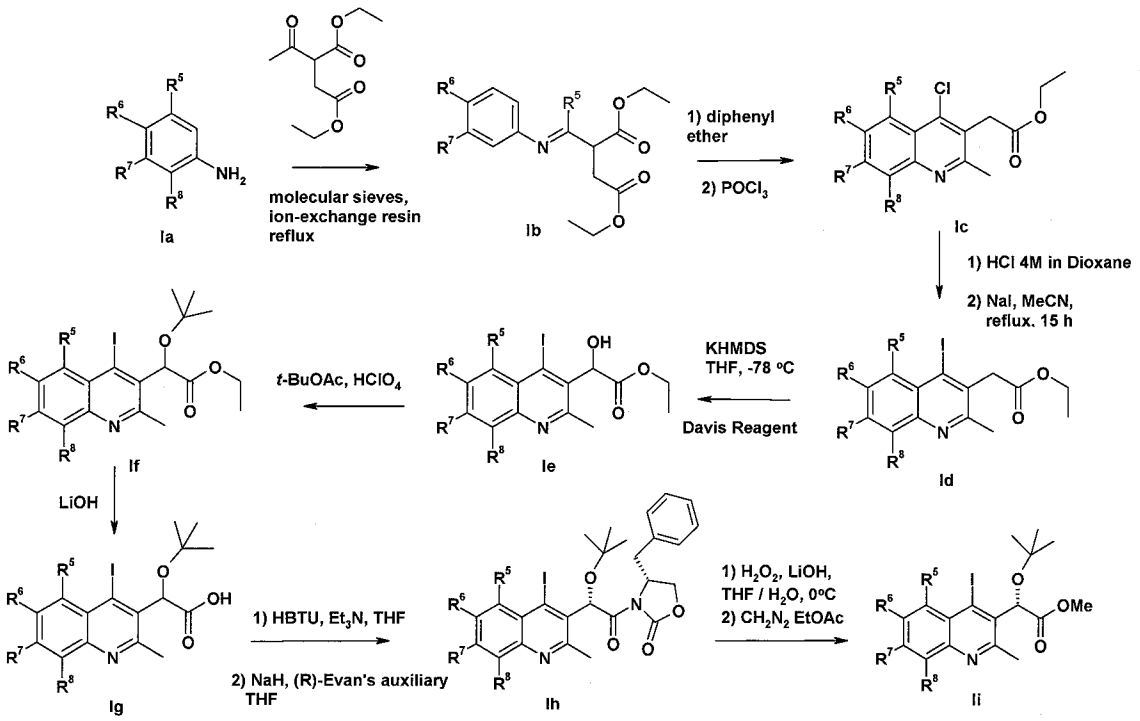
Additionally, intermediate III can be used for decarboxylative biaryl cross-coupling reactions similar to those described by Forgione, Bilodeau and coworkers, J. Am. Chem. Soc. **2006**, *128*, 11350-11351, herein incorporated by reference, as shown below:



Intermediate III **Intermediate V**

wherein **W** is iodo, bromo, chloro or OTf, R may be a substituent on the ring and P is as defined herein.

Scheme 1A

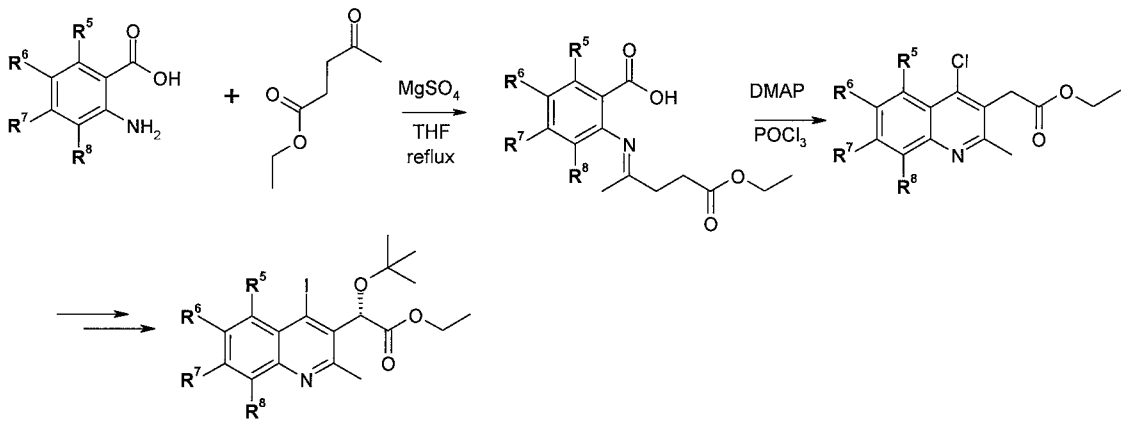


There are a number of transformations known to access quinoline scaffolds. As shown in Scheme 1A, a Friedlander approach can be followed in which appropriately substituted aniline is condensed with a functionalized ketone under dehydration conditions. This intermediate is then cyclized under thermal conditions followed by halogenation of the resulting alcohol. The acetic acid ester side chain can be oxidized and protected to furnish the alpha t-butoxy acetic acid ester moiety as shown. Separation of the enantiomers can be accomplished by formation of diastereomers by addition of a chiral auxiliary such as an oxazolidinone followed by

conversion to the corresponding ester by known means.

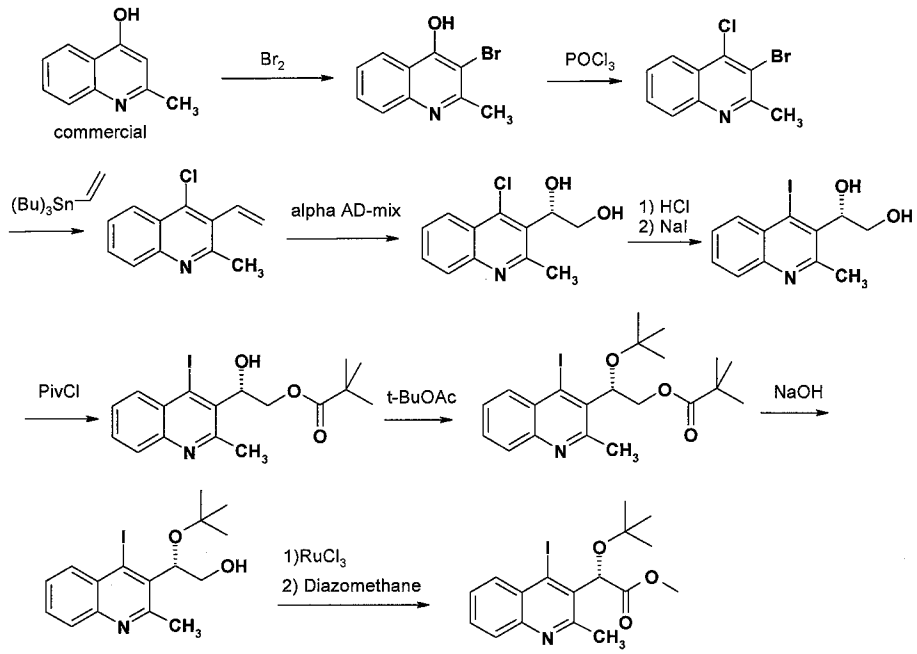
Alternatively, a modification of this approach can also be used to prepare the quinoline scaffold as is shown in Scheme 2. In this method a properly substituted anthranilic acid derivative can be condensed under dehydration conditions with an appropriate ketone and subsequently cyclized under DMAP/$POCl_3$ conditions to the 4-chloroquinoline. Further elaboration can then be performed as outlined in Scheme 1A.

Scheme 2:



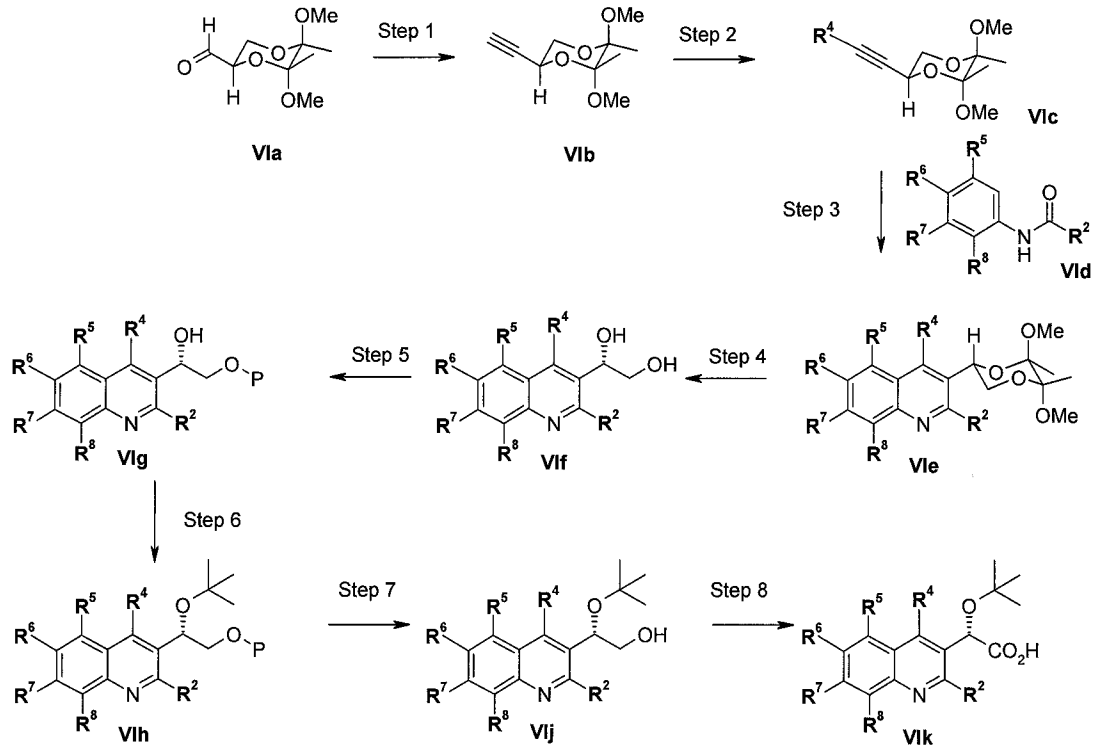
Furthermore, in an alternative route the quinoline scaffold can be accessed in an enantioselective manner as outlined in Scheme 3.

Scheme 3:



A quinoline precursor can be selectively brominated in the 3-position and subsequently elaborated into the chiral diol by standard methods known in the literature. The chiral diol can be differentially protected to the t-butyl ether followed by liberation of the primary alcohol. This alcohol can then be oxidized to the corresponding carboxylic acid and subsequently protected as the methyl ester to furnish the key chiral 4-iodoquinoline intermediate.

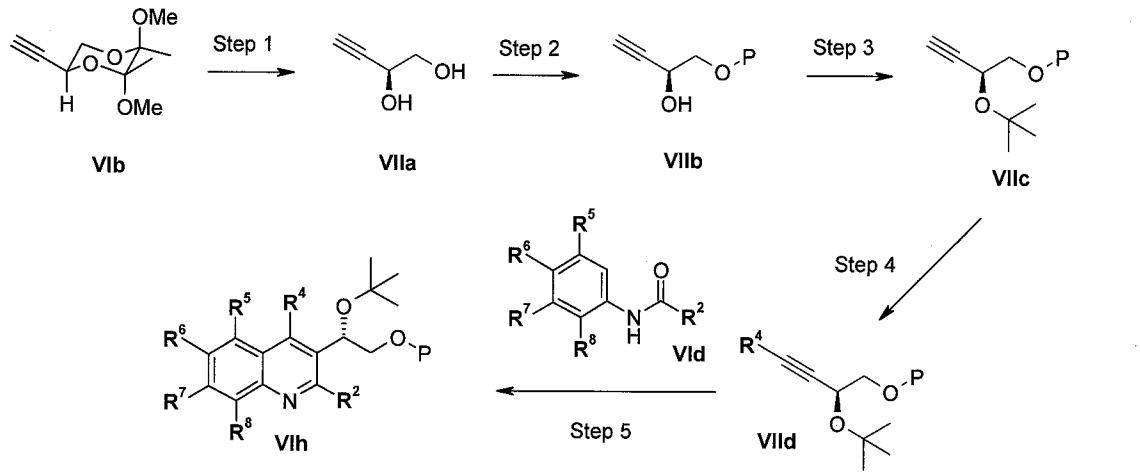
Scheme 4: Alternate synthesis of quinoline scaffold



In an alternate route to compounds of general formula I wherein R^2 is (C_{1-6})alkyl or –O- C_{1-6})alkyl, the known aldehyde **VIa** is transformed to terminal alkyne **VIb**. Those skilled in the art will recognize that there are a number of methods for accomplishing this transformation, such as, but not limited to the Bestmann-Ohira reaction or the Corey-Fuchs reaction. The R^4 group is then attached to the alkyne using conditions well-known to those skilled in the art, preferentially via a Sonogashira coupling between the alkyne and the aryl iodide derivative of the R^4 group, to give the internal alkyne **VIc**. Other methods may include the Castro-Stevens reaction, or the silver mediated, palladium catalyzed coupling of alkyne **VIb** and the boronic acid or ester derivative of the R^4 fragment as reported by Zou and coworkers (*Tetrahedron Lett.* **2003**, *44*, 8709-8711). The internal alkyne **VIc** then undergoes a cyclocondensation with amide **VId** to give quinoline **VIe**. Those skilled in the art will recognize this may involve activation of amide **VId** to facilitate the overall condensation. This is preferentially achieved by the action of triflic anhydride and in the presence of 2-chloropyridine as described by Movassaghi (*J. Am. Chem. Soc.*, **129** (33), 10096 - 10097, *2007*), but may also be achieved in other ways. Amides **VId** are typically commercially available, although those skilled in the art will recognize that they are also easily obtained from commercially available aniline or nitro arene precursors.

The cyclic diketal is then hydrolyzed to give diol **VIf** under acidic conditions. The terminal alcohol is then protected to give **VIg**, where P can be a number of different protecting groups including, but not limited to, a trimethylacetyl group. The secondary alcohol is then derivatized with a *tert*-butyl group to give compound **VIh**. Those skilled in the art will recognize that this can be accomplished in more than one way, including an SN_1 reaction or acid catalyzed addition to isobutylene. The protecting group is then removed to give primary alcohol **VIj**, which in turn is oxidized to carboxylic acid **VIk**. It will be obvious that the oxidation of **VIj** to **VIk** can be accomplished in one or two synthetic steps. In the preferred method, Dess-Martin oxidation to an intermediate aldehyde followed by Lindgren oxidation is employed.

Scheme 5: Alternate synthesis of quinoline scaffold



In yet another route to compounds of general formula **I,** wherein R^2 is (C_{1-6})alkyl or –O- C_{1-6})alkyl, synthesis of intermediate **VIh** may also be accomplished following a path that begins with acid catalyzed hydrolysis of the cyclic diketal of terminal alkyne **VIb** to give diol **VIIa**. The terminal alcohol is then protected to give **VIIb**, where P can be a number of different protecting groups including, but not limited to, a trimethylacetyl group. The secondary alcohol is then derivatized with the *tert*-butyl group to give compound **VIIc**. Those skilled in the art will recognize that this can be accomplished in more than one way, including an SN_1 reaction or acid catalyzed addition to isobutylene. The R^4 group is then attached to the alkyne using conditions well-known to those skilled in the art, preferentially via a Sonogashira coupling between the alkyne and the aryl iodide derivative of the R^4 group, to give the internal alkyne **VIId**. The internal alkyne **VIId** then undergoes a cyclocondensation with

amide **VId** to give quinoline **VIh**, preferentially achieved by the action of triflic anhydride and in the presence of 2-chloropyridine as described for step 3 of Scheme 4. From intermediate **VIh**, the synthesis of compounds of general formula **I** is then accomplished following steps 7 and 8 of Scheme 4.

EXAMPLES

Other features of the present invention will become apparent from the following non-limiting examples which illustrate, by way of example, the principles of the invention. It will be apparent to a skilled person that the procedures exemplified below may be used, with appropriate modifications, to prepare other compounds of the invention as described herein.

As is well known to a person skilled in the art, reactions are performed in an inert atmosphere (including but not limited to nitrogen or argon) where necessary to protect reaction components from air or moisture. Temperatures are given in degrees Celsius (°C). Solution percentages and ratios express a volume to volume relationship, unless stated otherwise. Flash chromatography is carried out on silica gel (SiO_2) according to the procedure of W.C. Still *et al.*, J. Org. Chem., (1978), 43, 2923. Mass spectral analyses are recorded using electrospray mass spectrometry. A number of intermediate and final products were are purified using CombiFlash® Companion apparatus, purchased from Teledyne Isco Inc, employing pre-packed silica gel cartridges and EtOAc and hexane as solvents. These cartridges are available either from Silicycle Inc (SiliaFlash, 40-63 microns silica) or from Teledyne Isco (RediSep, 40-63 microns silica). Preparative HPLC is carried out under standard conditions using a SunFire™ Prep C18 OBD 5µM reverse phase column, 19 x 50 mm and a linear gradient employing 0.1%TFA/acetonitrile and 0.1%TFA/water as solvents. Compounds are isolated as TFA salts when applicable. Analytical HPLC is carried out under standard conditions using a Combiscreen ODS-AQ C18 reverse phase column, YMC, 50 x 4.6 mm i.d., 5 µM, 120 Å at 220 nM, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	3.0	95	5
0.5	3.0	95	5
6.0	3.0	50	50

10.5	3.5	0	100

Abbreviations or symbols used herein include:

Ac: acetyl;
AcOH: acetic acid;
Ac_2O: acetic anhydride;
BOC or Boc: *tert*-butyloxycarbonyl;
Bu: butyl;
DABCO: 1,4-diazabicyclo[2.2.2]octane
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene;
DCE: dichloroethane;
DEAD: diethyl azodicarboxylate
DCM: dichloromethane;
DIAD: diisopropyl azodicarboxylate;
DIBAL: diisobutyl aluminum hydride;
DIPEA: diisopropylethylamine;
DMAP: N,N-dimethyl-4-aminopyridine;
DME: 1,2-dimethoxyethane;
DMF: *N,N*-dimethylformamide;
DMSO: dimethylsulfoxide;
Dppf: 1,1'-Bis(diphenylphosphino)ferrocene;
EC_{50}: 50% effective concentration;
Et: ethyl;
Et_3N : triethylamine;
Et_2O: diethyl ether;
EtOAc: ethyl acetate;
EtOH: ethanol;
HATU: O-(7-Azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate;
HBTU: O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate;
HPLC: high performance liquid chromatography;
IC_{50}: 50% inhibitory concentration;
^{i}Pr or i-Pr: 1-methylethyl (*iso*-propyl);
KHMDS: potassium hexamethyl disilazane;

LiHMDS: lithium hexamethyldisilazide;

Me: methyl;

MeCN: acetonitrile;

MeOH: methanol;

MOI: multiplicity of infection;

MS: mass spectrometry (ES:electrospray);

n-BuONa: sodium n-butoxide

n-BuOH: n-butanol;

n-BuLI: n-butyllithium;

NMO: N-methylmorpholine-N-oxide;

NMR: nuclear magnetic resonance spectroscopy;

Ph: phenyl;

PhMe: toluene;

PG: protecting group;

PPh_3: triphenylphosphine;

Pr: propyl;

RPMI: Roswell Park Memorial Institute (cell culture medium);

RT: room temperature (approximately 18°C to 25°C);

SM: starting material;

tert-butyl or t-butyl: 1,1-dimethylethyl;

Tf: trifluoromethanesulfonyl;

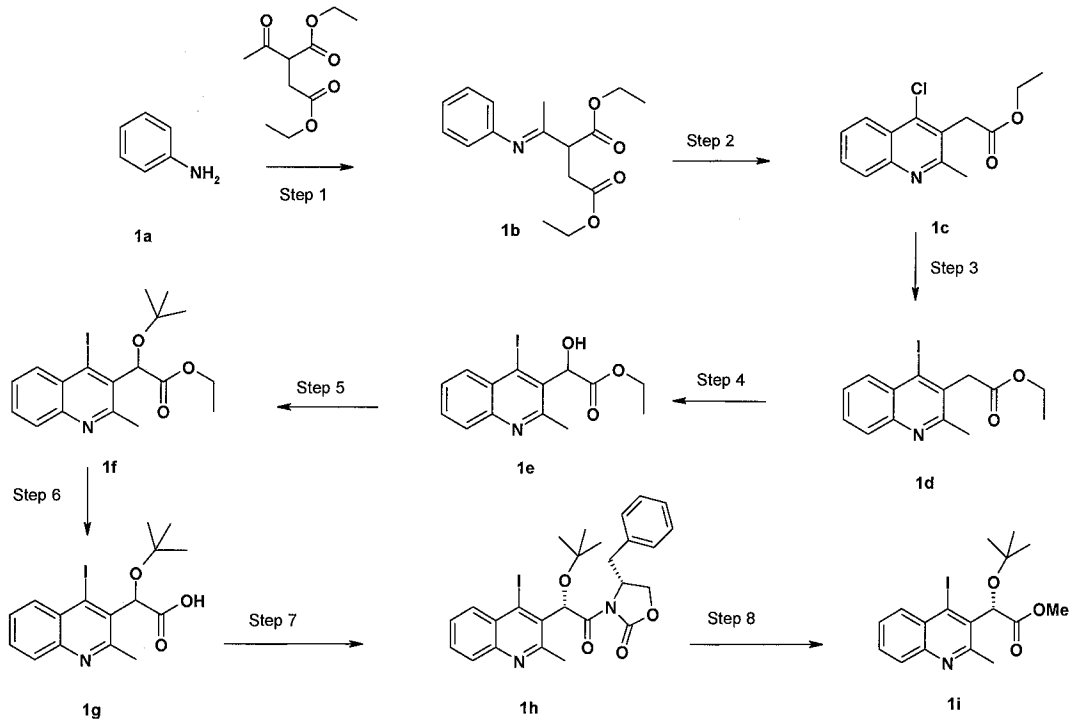
Tf_2O: trifluoromethanesulfonic anhydride;

TFA: trifluoroacetic acid;

THF: tetrahydrofuran; and

TLC: thin layer chromatography.

Example 1: Synthesis of quinoline scaffold **1i**



Step 1:

In a 4-neck 500 mL round bottom flask equipped with a magnetic stir bar, condenser and Dean-Stark trap, diethyl acetylsuccinate (6 g, 0.026 mol), aniline **1a** (2.5 mL, 0.028 mol), Amberlyst® 15 (0.08 g) and toluene (30 mL) are added. The resulting mixture is heated at reflux temperature for approximately 3 days at which time TLC showed only traces of SM. The reaction mixture is cooled to RT and the Amberlyst® 15 is removed by filtration. The filtrate is concentrated *in vacuo* to give a suspension of a solid in brown liquid. The filtrate is diluted with diethyl ether and cooled. The solid is filtered and the filtrate is concentrated *in vacuo* leaving a brown oil (~7.8 g), which contains **1b** and some cyclised intermediate. This crude intermediate is used in the next step without further purification.

Step 2:

In a 3-neck 100 mL round bottom flask a mixture of the crude intermediate **1b** (7.8 g) and diphenyl ether (50 mL) are heated quickly in a pre-heated (250°C) heating mantle for 6 min (internal temperature reached ~250°C) at which time the flask is removed from the heating mantle and is stirred until the internal temperature reaches below 100°C. The reaction mixture is then mixed with hexane (15 mL), at which time

a light brown solid is formed. The solid is filtered and washed with hexane (3 x 10 mL) to give approximately 2.4 g of the intermediate cyclised product. A portion of this sample (1.4 g, 5.87 mmol) is dissolved in phosphorus oxychloride (5 mL) and heated at reflux for 2.5 h. The reaction mixture is cooled to RT and is concentrated on vacuum. The residue is treated with sodium bicarbonate powder then partitioned between EtOAc and water. The combined organic layer is washed with brine, dried over anhydrous Na_2SO_4, filtered, passed through a silica gel pad and concentrated to give **1c** as a crude light brown solid (2.35 g).

Step 3:

Crude chloro quinoline **1c** (1.36 g, 5.17 mmol) is dissolved in THF (20 mL), and HCl in dioxane (4 M, 5.4 mL, 0.022 mol) is added to this solution slowly. The resulting reaction mixture is stirred at RT for 40 min. The solvent is then removed *in vacuo* and the residue is dried on vacuum. The resulting solid and NaI (3.87 g) are suspended in MeCN (20 mL), and the resulting reaction mixture is heated to reflux for 16 h. The reaction mixture is cooled to RT and treated with a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer is extracted with DCM, and the combined organic layer is dried over anhydrous $MgSO_4$, filtered and concentrated to give a brown syrup. Purification by silica gel chromatography (30% EtOAc/hexanes) provides iodo quinoline **1d** as an off-white solid (1.72 g, 94% yield).

Step 4:

To a solution of KHMDS (0.5 M in toluene, 3 mL, 1.5 mmol) in THF (8 mL) at -78°C is added a solution of **1d** (0.35 g, 0.99 mmol) in THF (8 mL). As the ester is added, the solution becomes a scarlet red. This is allowed to stir at -78 °C for 30 min before being treated with the Davis reagent (0.39 g, 1.5 mmol). After addition of the oxidizing agent, the solution becomes pale yellow and is stirred for an additional 30 min at -78°C. The reaction is quenched with saturated NH_4Cl aqueous solution (8 mL), is warmed to RT and is diluted with EtOAc. The mixture is washed with brine and the organic phase dried (Na_2SO_4), filtered and concentrated to afford a solid. Purification by silica gel chromatography (hexanes/EtOAc: 6/4) provides **1e** as a beige solid (0.50 g, >98% yield).

Step 5:

To a suspension of iodoalcohol **1e** (0.53 g, 1.4 mmol) in *tert*-butyl acetate (12 mL) at

RT is added perchloric acid (0.66 mL, 4.6 mmol). The reaction is left to stir for 2 h at RT (suspension turns into a clear solution). The reaction is quenched with water (12 mL) and basified with solid $NaHCO_3$ until pH ~ 6. The crude product is extracted with EtOAc (3 x 10 mL), washed with brine (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated to afford the crude product. Purification by silica gel chromatography (hexanes/EtOAc: 85/15) affords **1f** as a pale yellow oil (0.56 g, 91% yield).

Step 6:

Intermediate **1f** (0.59 g, 1.4 mmol) is dissolved in a 2 M NaOH aqueous solution (7 mL, 0.014 mol) with ethanol (10 mL) and is stirred for 4 h at RT. The ethanol is then removed *in vacuo*. The resulting residue is diluted with water (3 mL) and acidified with 2 M HCl solution until pH ~ 3-4. The residue is then extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4, filtered, concentrated and dried under high vacuum to afford **1g** as a foamy solid (0.56 g, >98% yield).

Step 7:

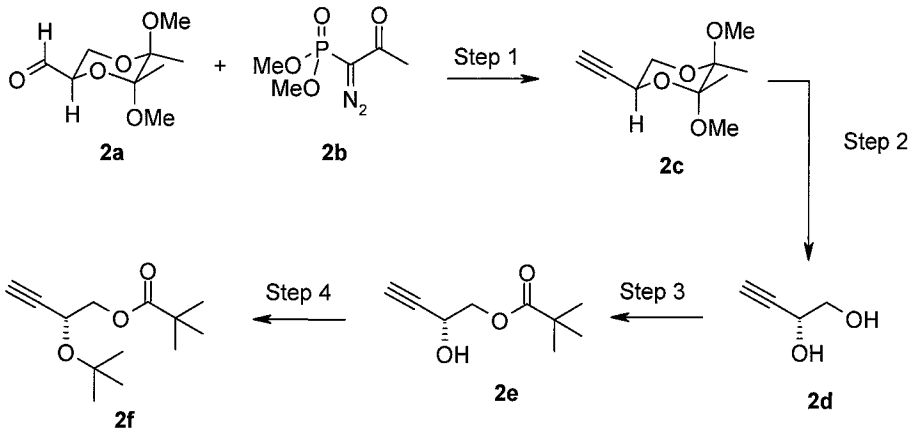
To a solution of acid **1g** (0.39 g, 0.97 mmol) and HBTU (0.48 g, ~1.3 mmol) in anhydrous THF (5 mL) is added diisopropylethylamine (0.5 mL, 2.9 mmol). The mixture is stirred for 5.5 h at 30-35°C (internal temperature) at which time the sodium salt of R-(+)-benzyloxazolidinone (which is prepared by adding sodium hydride (60% dispersion in mineral oil, 78 mg, 1.95 mmol) to a solution of R-(+)-benzyloxazolidinone (0.35 g, 1.9 mmol) in anhydrous THF (5 mL) is added. The resulting solution is then stirred at RT for 16 h. The solvent is removed *in vacuo* and partitioned between water and EtOAc. The aqueous phase is then extracted with EtOAc, and the combined organic extracts are dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow solid. The crude product is purified by silica gel chromatography (10->30% EtOAc:hexanes), yielding the desired diastereomer **1h** (190 mg, 35% yield, more polar product, >99% ee by chiral column).

Step 8:

To a solution of oxazolidinone **1h** (190 mg, 0.34 mmol) in THF/H_2O (2 mL/1 mL) at 0°C is added H_2O_2 (30%, 0.36 mL, 10.5 eq) followed by LiOH monohydrate (17 mg, 0.41 mmol, 1.2 eq) dissolved in water (1 mL). The reaction mixture is stirred at 0°C

for 30 min at which time 10% Na_2SO_3 (0.26 mL) is added. The resulting mixture is stirred for ~10 min and then acidified with 2 N HCl to pH ~4-5. The product is then extracted with DCM (3 x 10 mL). The combined organic extracts are dried over sodium sulfate and concentrated *in vacuo* to yield the crude acid intermediate as a white foam (0.13 g, 96% yield), which is used in the next step without further purification. The acid (130 mg) is suspended in diethyl ether (3 mL) and treated with diazomethane in diethyl ether until all of the acid SM is consumed (as indicated by TLC). The reaction is quenched with a very small amount of glacial AcOH and then concentrated *in vacuo* to give an off-white solid. The crude ester product is purified by silica gel chromatography (10-15% EtOAc/hexanes) yielding the quinoline fragment **1i** (120 mg, 89% yield) in high enantiomeric purity (>99% ee by chiral HPLC).

Example 2: Synthesis of fragment **2f**



Step 1:

Aldehyde **2a** (5.85 g, 28.6 mmol, for preparation see: Michel, P. and Ley, S. V. *Synthesis* **2003**, *10*, 1598-1602), phoshonate **2b** (6.6 g, 34 mmol) and K_2CO_3 (8.8 g, 64 mmol) are combined in MeOH (125 mL) and the reaction is stirred overnight at RT. The reaction is evaporated nearly to dryness and the residue is partitioned between H_2O (250 mL) and EtOAc (500 mL). The water layer is washed with EtOAc (2 x 250 mL) and the combined organic layers dried over anhydrous Na_2SO_4 and concentrated to give alkyne **2c** (5.55 g, 97% yield).

Step 2:

Alkyne **2c** (5.0 g, 25 mmol) is dissolved in TFA (35 mL) and water (3.6 mL) and the

solution is stirred at RT. After 30 min, the reaction is concentrated under reduced pressure and the residue is purified by CombiFlash® Companion to give diol **2d** (1.8 g, 84% yield).

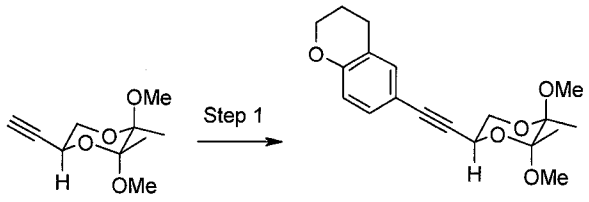
Step 3:

A solution of diol **2d** (1.2 g, 14 mmol) and triethylamine (1.7 mL, 12 mmol) in DCM (80 mL) is cooled to 0°C under N_2. Trimethylacetylchloride is added dropwise and the resulting mixture is allowed to come to RT and stir overnight. The reaction is then quenched with MeOH (100 mL) and stirring is continued for 20 min. The mixture is then concentrated under reduced under pressure and the residue is purified by CombiFlash® Companion to give the desired mono ester **2e** (550 mg, 40% yield) along with the undesired regioisomeric mono ester (378mg, 27% yield).

Step 4:

In a sealable reaction flask, a solution of the propargylic alcohol **2e** (375 mg, 2.20 mmol) and Amberlyst® H-15 resin (150 mg) in hexane (3 mL) is cooled to -78°C. Isobutene is then bubbled through the solution until the volume approximately doubles. The tube is then sealed, brought to RT and is stirred overnight. The tube is then cooled to -78°C, is opened and brought back to RT. The mixture is then filtered through a plug of SiO_2 (EtOAc wash) and concentrated under reduced pressure to provide pure *tert*-butyl ether **2f** (390 mg, 78% yield).

Example 3: Synthesis of alkyne **3a**



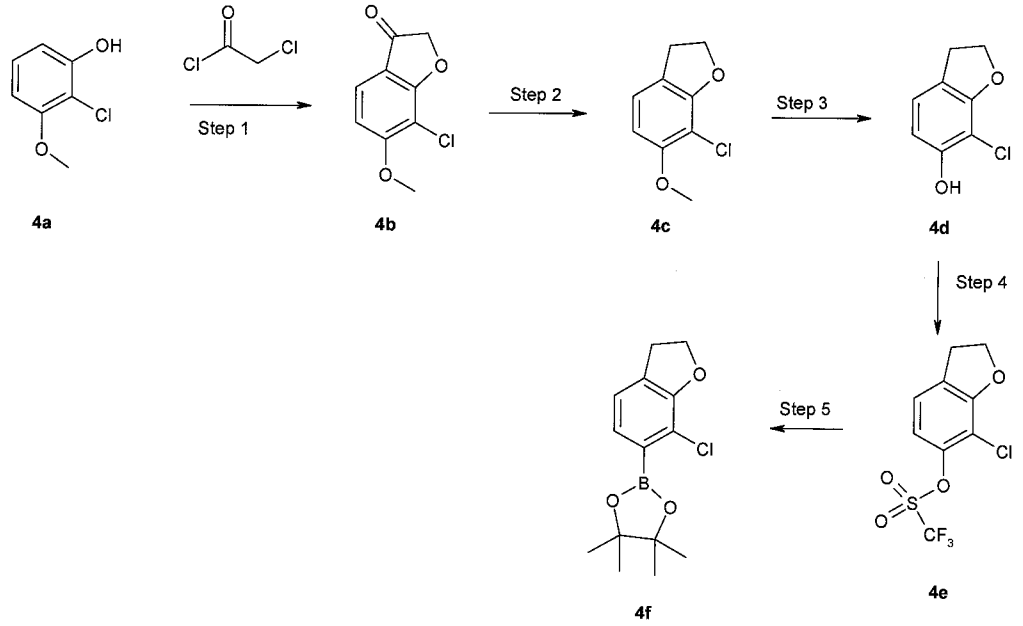
2c **3a**

Step 1:

Solid $Pd(PPh_3)_4$ (444 mg, 0.385 mmol) and CuI (146 mg, 0.769 mmol) are successively added to a solution of **11c** (10g, 34 mmol) and alkyne **2c** (11g, 55 mmol) dissolved in DMF (23 mL) and diethylamine (115 mL). The reaction mixture is stirred overnight at RT and then concentrated, diluted with EtOAc (300 mL) and

successively washed with brine, 1 N aqueous HCl and water (300 mL each). The organic layer is dried over Na_2SO_4 and the residue purified by CombiFlash® Companion to give alkyne **3a** (10.8 g, 84% yield).

Example 4: Synthesis of boronate fragment **4f**



Step 1:

To a solution of **4a** (6 g, 37 mmol) in nitrobenzene (12 mL), chloroacetyl chloride (4.6 mL, 57.5 mmol) is added, followed by the addition of $AlCl_3$ (20.4 g, 152 mmol). As the $AlCl_3$ is added, the mixture becomes viscous and gas evolution is observed. The resulting brown syrupy mixture is left to stir overnight at RT. (Reference: Y. Takeuchi et.al., *Chem.Pharm.Bull.* **1997**, *45(12),* 2011-2015.) The thick reaction mixture is cooled and ice water is added very carefully (Very exothermic) a few drops at a time. Once gas evolution and bubbling is subsided, cold water is further added followed by EtOAc. The mixture is stirred for 5 min and the product extracted with EtOAc (3x). The combined organic layers are washed with brine (1x), dried over Na_2SO_4, filtered and concentrated to afford the uncyclized chloroketone (24 g of crude; contaminated with some nitrobenzene) as a pale yellow solid. This intermediate is then taken up in EtOH (100 mL), NaOAc is added (20.4 g, 248 mmol) and the reaction is brought to reflux for 40 min. The EtOH is evaporated, the residue is taken up in EtOAc (300 mL) and washed with 5% K_2CO_3 (2 x 200 mL) and the aqueous layer then acidified with aqueous HCl (1 N; pH = ~5). This acidic layer is

extracted with EtOAc (2 x 250 mL), washed with brine (1x), dried over Na_2SO_4, filtered and concentrated to afford the crude product. This material is purified by CombiFlash® Companion (120 g) to afford intermediate **4b** as a yellow solid (4.7 g).

Step 2:

The ketone **4b** (127 mg, 0.64 mmol) is dissolved in EtOH (2 mL) and treated with hydrazine hydrate (500 µL, 16 mmol). The mixture is heated to reflux for 45 min before allowing it to cool to RT. The solvent is removed by evaporation and the residue is dissolved in diethylene glycol (1 mL) before being treated with KOH (108 mg, 1.92 mmol) and then heated to 110-120°C for 2.5 h. The reaction mixture is diluted with EtOAc and the pH is adjusted with 1 N HCl to pH <4. The organic phase is separated, washed with saturated brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude material is purified by CombiFlash® Companion (eluent: 0-50% EtOAc/hexanes) to give intermediate **4c** as a yellow oil (62 mg).

Step 3:

A solution of **4c** (61 mg, 0.33 mmol) is cooled to -78°C in DCM (2 mL) and then treated with BBr_3 (1 M in DCM, 825 µL, 0.82 mmol). After ~15 min, the bath is removed and the reaction is allowed to reach RT. The reaction is then stirred for 1.5 h. The reaction is cooled to 0°C before quenching by the careful dropwise addition of water. The mixture is treated with saturated $NaHCO_3$ (to about pH = 8) and the phases separated. The organic phase is washed with saturated brine, dried over $MgSO_4$, filtered and concentrated to dryness. The product is purified by CombiFlash® Companion (0-50% EtOAc/hexanes) to give intermediate **4d** as colorless oil, which solidifies upon standing (40 mg, 71% yield).

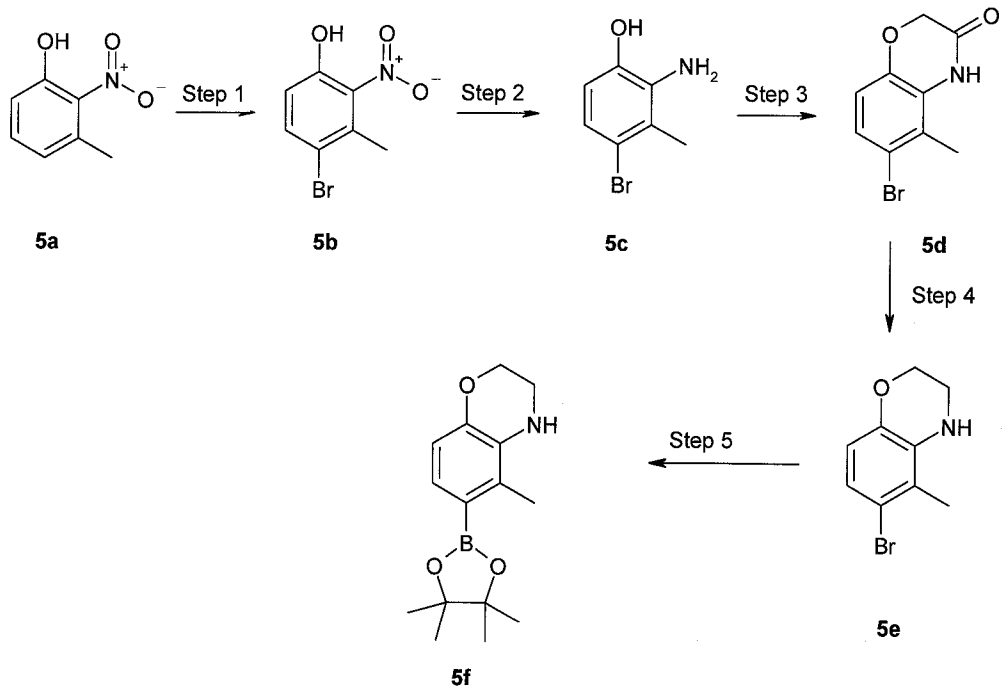
Step 4:

The phenol **4d** (40 mg, 0.23 mmol) is dissolved in DCM (2 mL), cooled to 0°C and treated with pyridine (95 µL, 1.17 mmol), followed by Tf_2O (44 µL, 0.26 mmol). The reaction is allowed to stir at this temperature for 10 min before warming to RT over a period of 1 h. The reaction mixture is diluted with DCM and the organic phase washed with 10% citric acid and then brine. The organic phase is dried over anhydrous $MgSO_4$, filtered, concentrated and purified by CombiFlash® Companion (0-50% EtOAc/ hexanes) to give **4e** as a yellow oil (67 mg, 94% yield).

Step 5:

To a solution of the triflate **4e** (66 mg, 0.22 mmol) in DMF (2 mL), bis-(pinacolato)diborane (72 mg, 0.28 mmol) and potassium acetate (64 mg, 0.65 mmol) are added. This solution is de-gassed (with bubbling Ar) for 10 min before adding $PdCl_2(dppf)$-CH_2Cl_2, (27 mg, 0.03 mmol, 0.15 eq). The mixture is de-gassed a further 5 min before being heated to 90°C for 16 h. The mixture is cooled to RT and diluted with EtOAc/water. The organic phase is washed with saturated brine (3x), dried over anhydrous $MgSO_4$, filtered and concentrated. The crude material is purified by CombiFlash® Companion (0-70% EtOAc in hexanes) to afford the boronate **4f** as a white solid (41 mg, 67% yield).

Example 5: Synthesis of boronate fragment **5f**



Step 1:

The nitrophenol **5a** (5.23 g, 34.1 mmol) is dissolved in acetic acid (20 mL) and the solution is cooled in an ice bath. Bromine (1.75 mL, 34.15 mmol) dissolved in 5 mL acetic acid) is added dropwise with stirring. The mixture is stirred for 1 h at 0°C before being poured into ice water (250 mL). The mixture is extracted with EtOAc (2 X 100 mL) and then washed with 5% $NaHCO_3$ (2 X 50 mL) before being dried over anhydrous $MgSO_4$, filtered and concentrated to give the desired crude product **5b** as an orange solid (8.2 g, quantitative yield). This material is used in the next step

without further purification.

Step 2:

To a well stirred ethanol solution (75 mL) of **5b** (8.1 g, 34.9 mmol), $SnCl_2$ (20 g, 105 mmol) is added. The reaction mixture is stirred at reflux for 2.5 h. After that period, the transformation is incomplete, therefore, more $SnCl_2$ (2g, 10 mmol) is added and the reaction mixture is heated at reflux for 1 h before being cooled to RT. The mixture is poured onto 250 g of ice and the pH adjusted to approximately 7.5 with aqueous 5% $NaHCO_3$. The product is extracted with EtOAc (3 X 100 mL) before being washed with saturated brine (2 X 100 mL). The organic phase is dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to give the aniline intermediate **5c** as a gray solid (8.25 g, ~100% yield; this material contained some tin residues, nonetheless, it is used as such for the following step).

Step 3:

To a stirring, ice cold, DMF (5 mL) suspension of potassium carbonate (2.05 g, 14.8 mmol) and aniline **5c** (750 mg, 3.71 mmol) under nitrogen, chloroacetyl chloride (355 µL, 4.45 mmol) is added dropwise. The mixture is allowed to warm to RT over a period of 15 min and then heated to 60°C for 1 h. The mixture is allowed to cool to RT, is poured into a mixture of ice/water (250 mL) and is stirred for approximately 15 min. The suspension is centrifuged, and the supernatant is discarded. The solid material is left drying under suction overnight to give intermediate **5d** (280 mg, 31% yield).

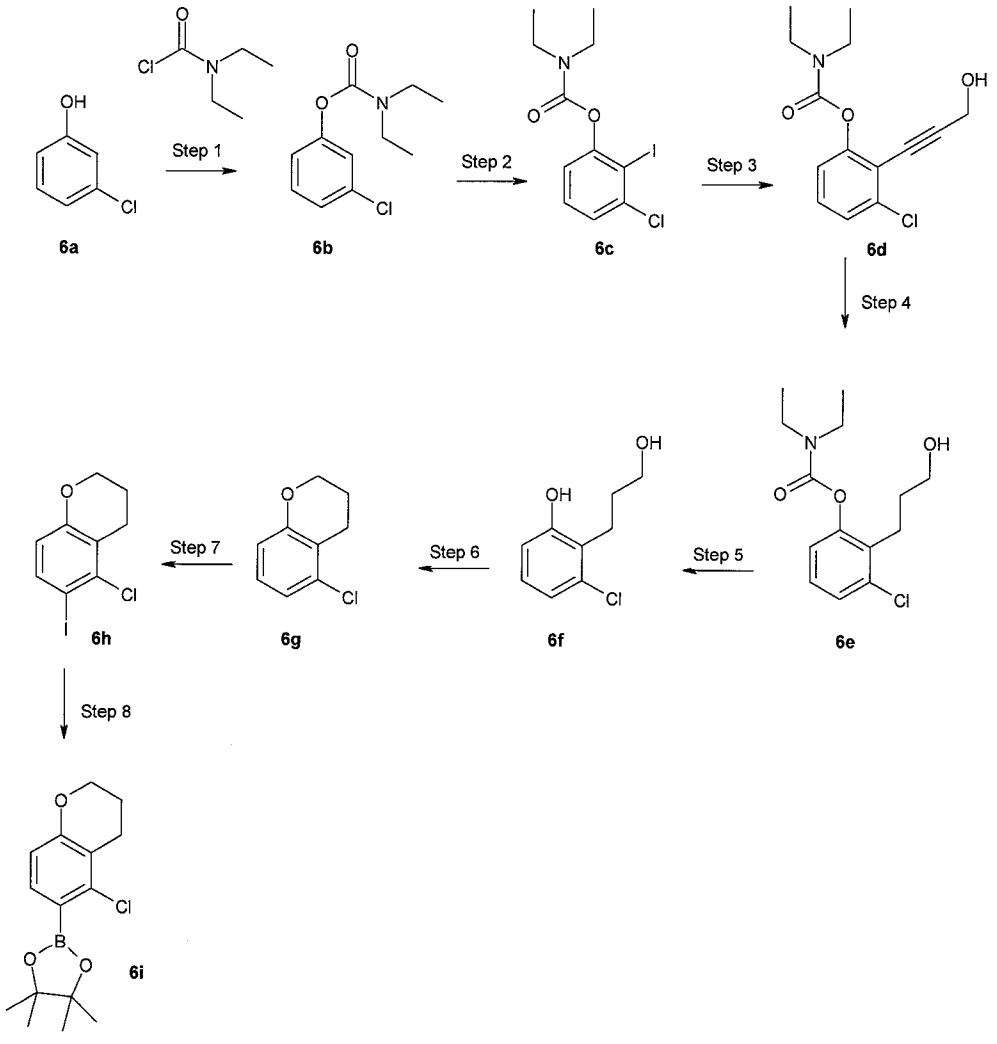
Step 4:

To an ice cold THF (6 mL) solution of the cyclic amide **5d** (280 mg, 1.16 mmol) under nitrogen, a borane-THF solution (1M in THF, 1.74 mL, 1.74 mmol) is added slowly. The reaction mixture is slowly allowed to warm to RT, then is stirred at RT for 1.5 h and then gently heated to reflux for 1 h to complete the conversion. The mixture is cooled in an ice bath and is carefully quenched with aqueous 1 M NaOH (4 mL) over 10 min. The reaction mixture is partitioned between EtOAc (150 mL) and water (25 mL). The organic layer is washed with aqueous 1 N NaOH (20 mL), saturated aqueous NaCl, and finally dried over anhydrous $MgSO_4$, filtered and concentrated to give the crude **5e** as an amber oil (212 mg, 81% yield). This product is used as such for next transformation.

Step 5:

A well stirred DMF (15 mL) solution of the arylbromide **5e** (0.50 g, 2.19 mmol), potassium acetate (0.728 g, 7.67 mmol) and bis(pinacolato)diborane (0.83 g, 3.3 mmol) is degassed by bubbling Ar through the solution for 20 min. $PdCl_2$(dppf)-DCM (320 mg, 0.44 mmol) is added and degassing is continued for 15 min. The system is sealed (teflon screw cap vessel) under Ar and heated to 90°C for 5 h. The reaction mixture is allowed to cool to RT, dilute with EtOAc (150 mL), washed with brine (3 x 100 mL) and water (2 x 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The residue is purified by CombiFlash® Companion (EtOAc/hexanes) to give the desired boronate **5f** (389 mg, 65% yield) as a yellowish waxy solid.

Example 6: Synthesis of boronate fragment **6i**



Step 1:

Sodium hydride (60%, 7.78 g, 194 mmol) is added to a well stirred suspension of **6a** (12.5 g, 97.2 mmol) in THF (100 mL). After stirring the reaction mixture for 1 h, N,N-diethylcarbamoyl chloride (24.64 mL, 194 mmol) is added at RT. After stirring the reaction overnight, the reaction mixture is quenched with water (100 mL), extracted with EtOAc (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to obtain **6b** (33 g, 75% yield) in high purity.

Step 2:

Diisopropylamine (21.0 mL, 121 mmol) in THF (330 mL) is treated with a solution of *n*-BuLi (2.5 M in hexanes, 48.2 mL, 121 mmol) at 0°C. After 30 min at this temperature, the solution is cooled to -78°C and carbamate **6b** (33.29 g, 109.7 mmol, 75 % pure) is added. The reaction is stirred at this temperature for 30 min and then iodine (33.4 g, 132 mmol) is added. The solution is stirred for 30 min at 0°C and is then warmed to RT. After 2 h, the reaction mixture is quenched with water (250 mL) and the volatile organic solvents are removed under reduced pressure. The aqueous phase is then extracted with EtOAc (3 x 100 mL), washed with 1 N HCl (1 x 200 mL), dry $MgSO_4$, filtered and evaporated under reduced pressure to obtain **6c** (18.6 g, 39% yield).

Step 3:

The iodo **6c** (10 g, 28 mmol), propargyl alcohol (3.3 mL, 56 mmol), $Pd(PPh_3)_4$ (3.27 g, 2.83 mmol) and copper iodide (1.08 g, 5.66 mmol) are combined in diisopropylamine (39 mL, 39 mmol) in a sealable tube under Ar and heated at 100°C. After 1 h, the reaction mixture is cooled to RT and poured into EtOAc (100mL) and this mixture is extracted with 10% HCl (2 x 100 mL). The organic layer is dried over $MgSO_4$ and concentrated to dryness. The crude product is purified by CombiFlash® Companion to obtain **6d** (3.65 g, 46% yield).

Step 4:

6d (3.63 g, 12.9 mmol) is dissolved in EtOAc (81 mL) and treated with Rh-Al_2O_3 (5% w/w, 3.45 g, 1.68 mmol). The flask is evacuated and charged with 1 atmosphere of H_2 (balloon) and the reaction is stirred overnight at RT. The reaction mixture is filtered through Celite® (EtOAc wash) and the filtrate is concentrated under reduced

pressure. The residue is then purified by CombiFlash® Companion to obtain **6e** (3.7 g, 71% yield).

Step 5:

Solid NaOH (920 mg, 23 mmol) is added to a solution of **6e** (2.63 g, 9.20 mmoL) in EtOH (93 mL) and the mixture is heated to reflux and is stirred overnight. The mixture is then cooled to RT and the organic solvent removed under reduced pressure. Water is added (100 mL) and the mixture extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain phenol **6f** (869 mg, 51% yield).

Step 6:

Diethyl azodicarboxylate (953 µL, 6.05 mmol) is added dropwise to a solution of phenol **6f** (869 mg, 4.66 mmol) and PPh_3 (1.59 g, 6.05 mmol) in THF (65 mL) and the reaction is stirred at RT. After 4 h, the reaction mixture is evaporated under reduced pressure. The residue is then purified by CombiFlash® Companion to obtain the chroman intermediate **6g** (387 mg, 49% yield).

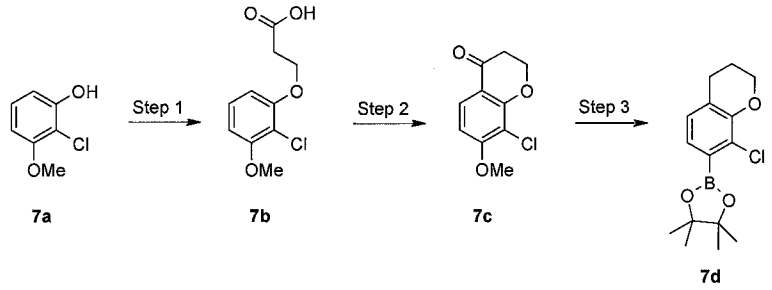
Step 7:

Iodine (583 mg, 2.29 mmol) is added to a solution of chroman **6g** (387 mg, 2.29 mmol) and $AgNO_3$ (429 mg, 2.52 mmol) in MeOH (23 mL). After 20 min, a 0.5 M solution of sodium thiosulfate (10 mL) is added and the aqueous phase extracted with EtOAc (3 x 25 mL). The combined organic phases are washed with brine, then dried ($MgSO_4$), filtered and evaporated to obtain aryl iodide **6h** (647 mg, 96% yield).

Step 8:

A solution of iodo intermediate **6h** (647 mg, 2.20 mmol), bis(pinocolato)diborane (0.725 g, 2.86 mmol) and potassium acetate (0.626 g, 6.59 mmol) in DMF (17 mL) is degassed with Ar for 10 min. $PdCl_2$(dppf)-DCM complex (179 mg, 0.22 mmol) is then added and the mixture is degassed with Ar for approximately another 5 min. The reaction is then heated to 95°C in a sealable tube and is stirred overnight. The reaction is cooled to RT and EtOAc (100 mL) is added. The solution is washed with brine (3 x 150 mL), water (1 x 150 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. The residue is purified by CombiFlash® Companion to afford boronate ester **6i** (260 mg, 40% yield).

Example 7: Synthesis of boronate fragment **7d**



Step 1:

A solution of phenol **7a** (0.91 g, 5.74 mmol) in dry DMF (1 mL) is added dropwise to a slurry of NaH (60% in oil, 0.60 g, 15 mmol) in dry DMF (1 mL) cooled to 10-15°C (cold water bath) and the mixture is stirred for 20 min. This results in a thick, frothy white mixture. A solution of 3-bromopropionic acid (1.1 g, 6.9 mmol) in dry DMF (0.5 mL) is then added dropwise and the reaction stirred at RT overnight. After 16 h, methanol (1.2 mL) is added to help break up the thick, pasty reaction mixture which is then added to diluted HCl (12 mL, 1 N HCl in 100 mL water) and extracted with EtOAc (80 mL; the pH of the aqueous phase is adjusted to pH <3). The organic layer is dried over anhydrous Na_2SO_4 and evaporated to give **7b** as a white solid material, contaminated with some unreacted SM (1.29 g of crude material). This material is used in the next step without purification.

Step 2:

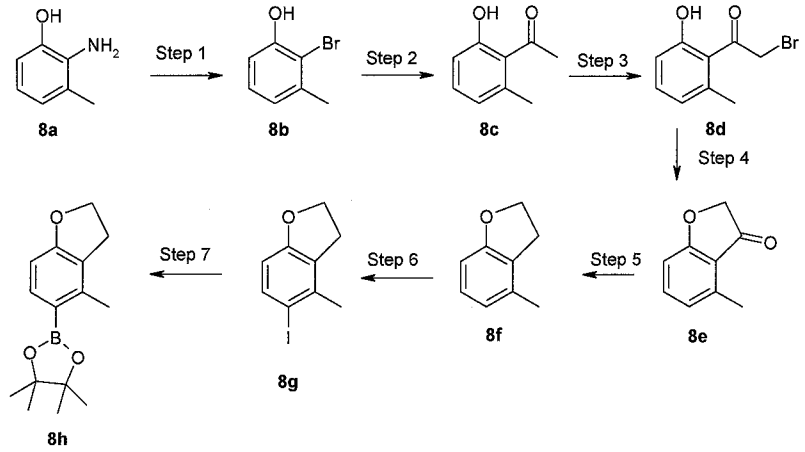
The crude compound **7b** (1.53 g, 6.63 mmol) is combined with polyphosphoric acid (approximately 7 g) and heated to 75°C to give a cherry red colored solution. During the reaction time, the reaction mixture becomes viscous and stirring becomes difficult. After 4 h, the reaction is cooled; ice and water are slowly added with rapid stirring to give a thick suspension. This mixture is transferred to a separatory funnel where the product is extracted with EtOAc (100 mL) and washed with water (100 mL), saturated $NaHCO_3$ (2 x 100 mL) and brine (75 mL). The organic phase is dried over anhydrous $MgSO_4$ and evaporated to give a sticky violet solid **7c** which is used as such (1.29 g crude).

Step 3:

Intermediate **7c** is analogous to intermediate **4b** in Example 4; those skilled in the art

would recognize that the same synthetic methodologies used to convert **4b** to the boronate **4f** can be applied for the conversion of **7c** to the corresponding boronate **7d**.

Example 8: Synthesis of boronate fragment **8h**



Step 1

2-Amino-*m*-cresol **8a** (5.7 g, 46.3 mmol) is dissolved in H_2O (30 mL) and 1,4-dioxan (15 mL). The mixture is heated to reflux and then HBr (48%, 17 mL, 0.31 mol) is added dropwise over a period of 20 min. The reflux is maintained for an additional 15 min after the addition is complete. The reaction is cooled to 0^oC, and $NaNO_2$ in H_2O (20 mL) is added over a period of 30 min. The stirring is continued for 15 min at 0^oC, the mixture is then transferred in one shot to a stirring mixture of Cu(I)Br (7.64 g, 53.2 mmol) in H_2O (20 mL) and HBr (48%, 17 mL, 0.31 mol) at 0^oC (protected from light). The reaction is stirred for 15 min at 0^oC, warmed to 60^oC, stirred for an additional 15 min, cooled to RT and then stirred overnight. The reaction mixture is then transferred to a separatory funnel and extracted with EtOAc (3x). The organic layers are combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated over silica to afford a mixture that is purified using the CombiFlash® Companion (20% EtOAc/hexanes) to afford the desired bromide **8b** (1.46 g, 17% yield) as a red-brown oil.

Step 2:

To a solution of the bromide **8b** (1.36 g, 7.27 mmol) and $(PPh_3)_2PdCl_2$ (766 mg, 1.09 mmol) in DMF (12 mL), 1-ethoxyvinyl-tri-n-butyltin (2.7 mL, 8.0 mmol) is added. The

mixture is capped and heated in a microwave at 160°C for 15 min. HPLC and LC-MS analysis indicate approximately 70% conversion. More 1-ethoxyvinyl-tri-n-butyltin (2.7 mL; 8.0 mmol) and catalyst $(PPh_3)_2PdCl_2$ (380 mg) are added and the solution is again subjected to the same microwave conditions. The reaction is quenched with 6N HCl (1.5 mL) and stirred at RT for 1 h to effect hydrolysis of the intermediate. The mixture is poured into EtOAc (150 mL), washed with brine (3x), dried over $MgSO_4$, filtered and concentrated over silica to afford the mixture that is purified using the CombiFlash® Companion (20% EtOAc/hexanes) to afford the desired ketone **8c** (947 mg, 87% yield) as an orange oil.

Step 3:

The methyl ketone **8c** (1.02 g, 6.8 mmol) is dissolved in EtOAc (15 mL) and $CHCl_3$ (15 mL) before being treated with $Cu(II)Br_2$ (3.03 g, 13.6 mmol). The mixture is heated to reflux for 16 h. The mixture is cooled to RT, the product filtered and washed with EtOAc (1x). The solution is concentrated over silica to afford the mixture that is purified using the CombiFlash® Companion (10% EtOAc/hexanes) to afford the α-bromoketone **8d** (710 mg, 46% yield) as an orange oil. This material is used as is in the next step without purification.

Step 4:

To a solution of the bromoketone **8d** (710 mg, 3.1 mmol) in anhydrous DMF (12 mL), KF (400 mg, 6.95 mmol) is added. The reaction is stirred at RT for 16 h. The mixture is taken up in EtOAc (150 mL), washed with brine (3x), dried over anhydrous $MgSO_4$, filtered and concentrated over silica to afford the mixture that is purified using the CombiFlash® Companion (20% EtOAc/hexanes) to afford the cyclic ketone **8e** (280 mg, 61% yield) as a pale orange solid.

Step 5:

Zn dust pre-activation procedure: Zinc dust (20 g, 350 mesh) is placed in a round bottom flask and 1 N HCl (50 mL) is added. This suspension is sonicated for 1 min before decanting off the liquid. This procedure is repeated for a second time after which the solid is washed with EtOH (2x), Et_2O (2x) and dried under high vacuum. To a solution of the ketone **8e** (280 mg, 1.89 mmol) in AcOH (10 mL) pre-activated Zn dust (1.24 g, 18.9 mmol) is added. The reaction mixture is then heated to 75°C for 2 h. The reaction mixture is filtered (with EtOAc washing of the solids). The

solvent is evaporated over silica and the mixture is directly purified using the CombiFlash® Companion (10% EtOAc/hexanes) to afford the desired dihyrobenzofuran **8f** (174 mg, 69% yield) as a colorless oil.

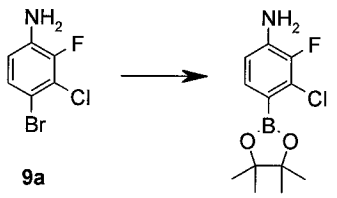
Step 6:

To a solution of the dihydrobenzofuran **8f** (240 mg, 1.8 mmol) in MeOH (5 mL), $AgNO_3$ (304 mg, 1.79 mmol) is added followed by iodine (453 mg, 1.79 mmol). The yellow mixture is stirred at RT for 1 h. To the reaction mixture is added a solution of 10% $Na_2S_2O_3$ and the mixture is stirred for 15 min at RT. The mixture is diluted with EtOAc (100 mL), and the organic layer is washed with brine (3x) and 10% $Na_2S_2O_3$ (2x). The organic phase is dried over anhydrous $MgSO_4$, filtered and concentrated over silica to give a mixture. This mixture is purified using the CombiFlash® Companion (10% EtOAc/hexanes) to afford the iodo derivative **8g** (400 mg, 86% yield) as a white amorphous solid.

Step 7:

A mixture of the iodo derivative **8g** (400 mg, 1.54 mmol), bis(pinocolato)diborane (585 mg, 2.31 mmol), potassium acetate (511 mg, 5.4 mmol) in DMF (20 mL) is degassed (Ar balloon and sonication for 5 min); then the catalyst ($PdCl_2$dppf, 188 mg, 0.23 mmol) is added with additional degassing (Ar balloon and sonication for 2 min). The mixture is then heated to approximately 95°C for 4 h. The mixture is cooled, EtOAc (200 mL) is added, washed with brine (3x), water (2x), dried over anhydrous $MgSO_4$, filtered and solvent evaporation over silica affords the mixture that is purified using the CombiFlash® Companion (10 % EtOAc/hexanes) to afford the desired boronate **8h** (315 mg, 79% yield) as a yellow oil.

Example 9: Synthesis of boronate fragment **9b**

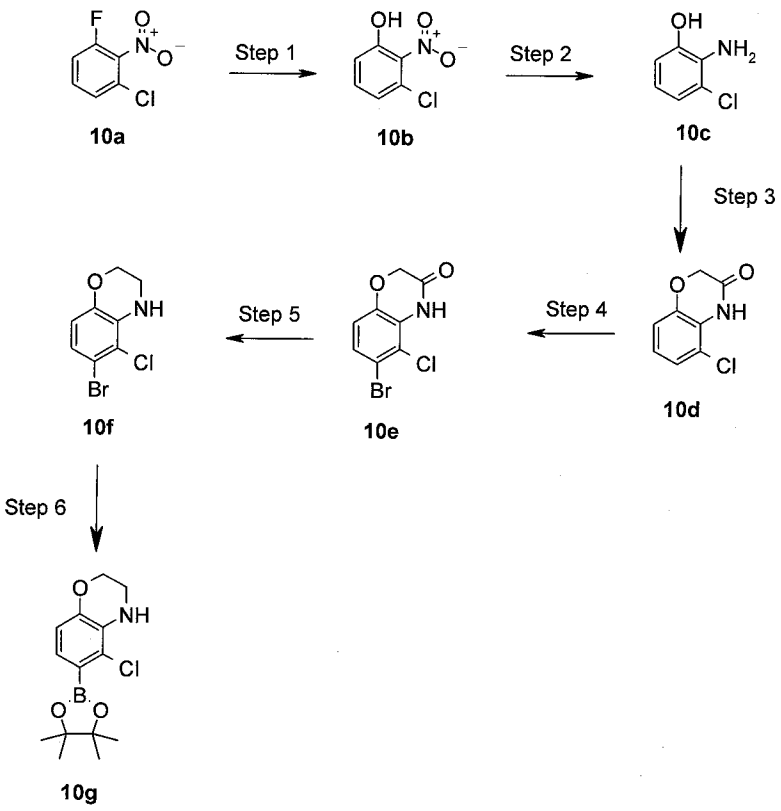


9a **9b**

Anhydrous DMF (60 mL) is added to a flask charged with bromide **9a** (5.00 g, 22.2

mmol), *bis*-(pinacolato)diborane (8.48 g, 33.4 mmol) and potassium acetate (6.35 g, 66.8 mmol) and the resulting suspension is deoxygenated by bubbling a stream of N_2 gas through the mixture for 45 min. 1,1'-bis(diphenylphosphino)ferrocene (2.73 g, 3.34 mmol) is then added and the mixture is deoxygenated for approximately a further 5 min and is then heated to 95°C. After 16 h, the dark reaction mixture is cooled, extracted with EtOAc (500 mL and 300 mL) and washed with 1:1 water/brine (600 mL) and brine (600 mL). The combined extracts are dried over anhydrous $MgSO_4$, filtered and evaporated to a black syrup which is purified by flash column chromatography (EtOAc / hexane) to afford the boronate **9b** as white solid contaminated with <25 % of the diboron reagent (4.24 g, 62% yield).

Example 10: Synthesis of boronate fragment **10g**



Step 1:

2-Chloro-6-fluoronitrobenzene **10a** (6.62 g, 37.7 mmol) and LiOH monohydrate (6.33 g, 151 mmol) are dissolved in THF (45 mL) and water (65 mL) and an aqueous solution of H_2O_2 (30%, 8.60 mL, 80.0 mmol) added. The resulting turbid solution is

sealed and is heated to 60°C with rapid stirring. After 3 days, the dark orange mixture is cooled and is added to half-saturated aqueous sodium thiosulfate (200 mL) and shaken vigorously in a separatory funnel. The mixture is then acidified to pH < 3 with 1 N HCl, extracted with EtOAc (500 mL) and washed with brine (400 mL). The combined extracts are dried over magnesium sulfate, filtered and evaporated to a deep yellow oil (aminophenol **10b**) containing some solid particles (residual starting material) which is used as such (6.37 g, 97% yield).

Step 2:

The crude aminophenol **10b** (6.37 g, 36.7 mmol) is dissolved in THF (100 mL) and tin powder (17.4 g, 147 mmol) is added followed by 1 N HCl (220 mL, 220 mmol). The resulting mixture is stirred vigorously at RT. After 16 h, the reaction is cooled to 0°C, the acid neutralized with 10 N NaOH (22 mL) and the resulting milky suspension stirred vigorously for 15 min. The mixture is then filtered through a pad of Celite® and the solids washed thoroughly with EtOAc (4 x 200 mL). The filtrate is transferred to a separatory funnel and the aqueous phase acidified with 1 N HCl (4 mL), diluted with brine (400 mL) and the organic phase washed with brine (400 mL). The extract is then dried over sodium sulfate, filtered and evaporated to afford aminophenol **10c** as a waxy, pale brown solid (2.91 g, 55% yield).

Step 3:

Chloroacetyl chloride (1.94 mL, 24.3 mmol) is added to an ice-cold mixture of aminophenol **10c** (2.91 g, 20.3 mmol) and potassium carbonate (8.40 g, 60.8 mmol) in anhydrous DMF (200 mL) under a N_2 atmosphere. After 5 min, the reaction is allowed to warm to RT and, after a further 45 min, is heated to 50°C. After 15 h, the reaction is cooled and extracted with EtOAc (600 mL) and washed with water/brine (1 L), half-saturated sodium bicarbonate (1 L) and brine (600 mL). The organic phase is then dried over $MgSO_4$, filtered and evaporated to afford lactam **10d** as a fibrous, pale-olive solid (3.15 g, 85% yield).

Step 4:

Bromine (1.8 mL; 35 mmol) is slowly added dropwise to a stirred solution of lactam **10d** (3.15 g; 17.1 mmol) in anhydrous DCM (40 mL) at RT. After 3 h, the resulting suspension is slowly added to saturated aqueous sodium thiosulfate (200 mL) and extracted with DCM (4 x 100 mL). The combined extracts are then washed with

brine (200 mL), dried over magnesium sulfate, filtered and evaporated to afford the bromide **10e** as a pale beige powder (4.00 g, 89% yield).

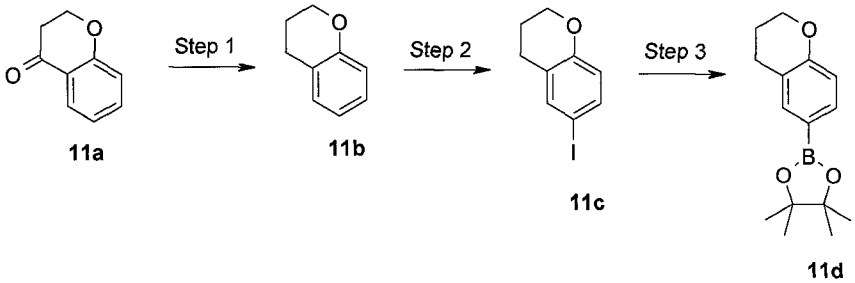
Step 5:

A solution of borane in THF (1.0 M, 18.5 mL, 18.5 mmol) is added dropwise to an ice-cold solution of lactam **10e** (4.00 g, 15.2 mmol) in anhydrous THF (75 mL), and the reaction is allowed to warm to RT. After 30 min, the solution is heated to gentle reflux under a N_2 atmosphere. After 2 h, the reaction is cooled to 0°C and carefully quenched with 1 N NaOH (19 mL) and stirred for 15 min. The mixture is then diluted with water (30 mL) and the THF is evaporated. The aqueous residue is then extracted with EtOAc (400 mL + 50 mL) and washed with water/brine (200 mL), 0.5 N NaOH (200 mL) and brine (100 mL). The combined extracts are dried over magnesium sulfate, filtered and evaporated to afford the morpholine derivative **10f** as a yellow syrup (3.90 g, quantitative yield).

Step 6:

Anhydrous DMF (30 mL) is added to a flask charged with aryl bromide **10f** (1.84 g, 7.42 mmol), *bis*(pinacolato)diborane (2.83 g, 11.1 mmol) and potassium acetate (2.47 g, 26.0 mmol) and the resulting suspension is then deoxygenated by bubbling a stream of N_2 gas through the mixture for 15 min. 1,1'-bis(diphenylphosphino)ferrocene (909 mg, 1.11 mmol) is then added and the mixture is deoxygenated for a further 5 min and then heated to 95°C. After 16 h, the dark reaction mixture is cooled, diluted with EtOAc (300 mL) and washed with 1:1 water/brine (500 mL) and brine (200 mL). The extract is then dried over $MgSO_4$, filtered and evaporated to a brown syrup which is chromatographed over silica gel (EtOAc/hexanes) to afford the boronate **10g** as a white solid contaminated with 0.8 eq of the diboron reagent (1.52 g, 69% yield).

Example 11: Synthesis of boronate fragment **11d**



Step 1:

Commercially available chromanone **11a** (9.78 g, 66.0 mmol) dissolved in AcOH (20 mL) is added to a suspension of zinc dust (108 g, 1.65 mol) in AcOH (150 mL). The mixture is heated to 100°C and is stirred mechanically overnight. The mixture is then filtered through Celite® (washed with EtOAc, 100mL), diluted with PhMe (300 mL) and the solution is evaporated to give chroman intermediate **11b** (8.45 g, 95% yield).

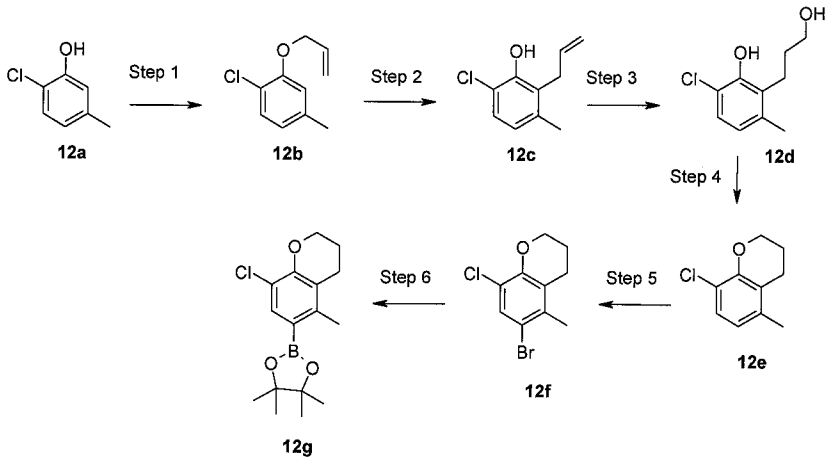
Step 2:

$AgNO_3$ (12.0 g, 70.6 mmol) and I_2 (15.8 g, 62.3 mmol) are added sequentially to a solution of **11b** (8.45 g, 63.0 mmol) dissolved in MeOH (225 mL). The reaction is allowed to stir for 1 h, filtered on Celite® and the filtrate concentrated under reduced pressure. The crude mixture is diluted with EtOAc (250 mL) and washed with saturated sodium thiosulfate (250 mL). The organic layer is washed with water (200 mL) and then dried over Na_2SO_4, filtered and concentrated. The crude mixture is further purified by CombiFlash® Companion to give 6-iodochroman **11c** (12.1 g, 74% yield).

Step 3:

A solution of the 6-iodochroman **11c** (1.0 g, 3.85 mmol), bis[pinocolato]diborane (1.22 g, 4.81 mmol) and potassium acetate (1.10 g, 11.5 mmol) in DMF (36 mL) is degassed with Ar for 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (314 mg, 0.38 mmol). The reaction mixture is then degassed for an additional 5 min before being heated to 95°C for 5 h. The reaction is then cooled to RT. The crude reaction mixture is diluted with water and the product is extracted with EtOAc (3 x 100 mL). The combined organics are washed with water (100 mL) and brine (100 mL). The organic phase is then dried over $MgSO_4$ and filtered and concentrated. The crude mixture is further purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to afford the borane fragment **11d** (840 mg, 84% yield).

Example 12: Synthesis of boronate fragment **12g**



Step 1:

The phenol **12a** (6.75 g, 47.3 mmol) is dissolved in DMF (270 mL) and is treated with allyl bromide (6.55 mL, 75.7 mmol). To this solution, NaH (60%, 4 g, 99.4 mmol) is added portionwise and stirring is continued overnight. The reaction mixture is diluted with EtOAc (500 mL) and washed with H_2O (3 x 500 mL). The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness to obtain the desired product **12b**, which is used as such in the next step.

Step 2:

The ether **12b** (9.67 g) is placed in a microwave vial neat with a stir bar and is heated to 240°C for 20 min at which point the Claisen rearrangement reaction is complete. The crude product **12c** (9.3 g) is used in the following step without further purification.

Step 3:

To a solution of the allyl intermediate **12c** (9.3 g, 45.8 mmol) in anhydrous THF (300 mL) at 0°C, borane (1 M in THF, 96 mL, 96 mmol, 2.1 eq) is added. The solution is allowed to warm to RT and then is stirred for 2.5 h. The solution is then cooled to 0°C and treated with 10 N NaOH dropwise, followed by slow addition of 30% H_2O_2 (104 ml, 916 mmol). The resulting mixture is allowed to warm to RT and then is stirred at RT for 1 h. The reaction mixture is diluted with HCl (10%, 100mL) and extracted with EtOAc (3 x 200mL). The combined organic phases are dried over $MgSO_4$ and concentrated. The crude product is purified by CombiFlash® Companion to give **12d** (7.1 g, 77% yield).

Step 4:

To a solution of the diol **12d** (7.1 g, 35.3 mmol) in THF (500 mL), PPh_3 (12 g, 45.9 mmol), followed by DEAD (7.2 mL, 45.9 mmol) are added. The solution is stirred at RT for 4 h. The reaction mixture is evaporated under reduced pressure and purified by CombiFlash® Companion to obtain the desired product **12e** (5.26 g, 82% yield).

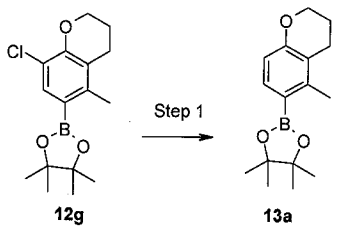
Step 5:

The chroman derivative **12e** (5.26 g, 28.8 mmol) is dissolved in AcOH (70 mL) and is then treated with Br_2 in AcOH (40 mL). The reaction is stirred at RT for 15 min, then diluted with toluene and concentrated to dryness. The residue is taken up in EtOAc (25 mL) and washed with saturated $Na_2S_2O_3$ (25 mL) and saturated $NaHCO_3$ (25 mL). The organic layer is dried over $MgSO_4$, concentrated and purified by CombiFlash® Companion to obtain the desired product **12f** (2.7 g, 36% yield).

Step 6:

The bromide **12f** (2.71 g, 10.4 mmol) is dissolved in DMF (120 mL) and treated with bispinocolatoborane (4 g, 15.5 mmol) and potassium acetate (3.45 g, 36.3 mmol). The mixture is degassed (using an Ar balloon) before the introduction of the catalyst ($PdCl_2$dppf, 845 mg, 1.04 mmol). The mixture is then degassed again (using an Ar balloon) and heated to 95°C for 16 h. The mixture is cooled to RT, diluted with H_2O (300 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers are washed with water (3 x 300 mL) dried over $MgSO_4$, filtered and concentrated. The product is then purified by CombiFlash® Companion. The semi-purified product is then triturated with hexanes (3x 50 mL) in order to remove the excess disborane and obtain clean compound **12g** (1.74 g, 54% yield).

Example 13: Synthesis of boronate fragment **13a**

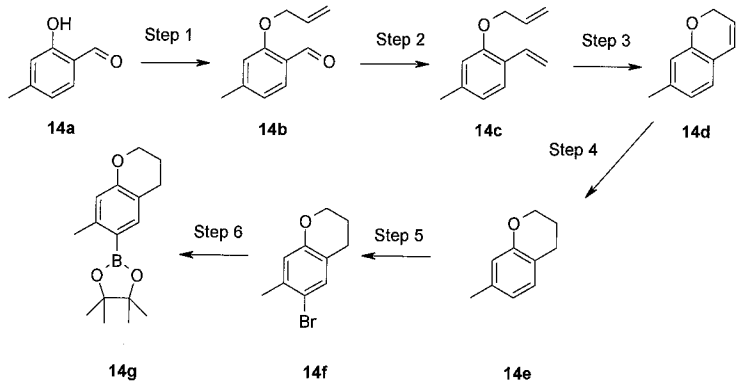


12g **13a**

Step 1:

Palladium on activated charcoal (10% Pd by weight, 0.63 mg, 0.59 mmol) is added to a solution of aryl chloride **12g** (0.91 g, 2.95 mmol) and ammonium formate (1.92 g, 30.4 mmol) dissolved in MeOH and the mixture is heated to reflux. After 15 min, the reaction is cooled to RT and filtered through Celite® (MeOH rinse). The filtrate is evaporated to dryness and the residue partitioned between water and EtOAc (10 mL each). The organic layer is dried over anhydrous $MgSO_4$ and concentrated to obtain boronic ester **13a** (0.78 g, 97% yield).

Example 14: Synthesis of boronate fragment **14g**



Step 1:

Allyl bromide (9.3 mL, 110 mmol) followed by potassium carbonate (20 g, 150 mmol) are added to a solution of **14a** (10 g, 73 mmol) dissolved in DMF (110 mL). The reaction is allowed to stir under Ar at RT overnight. The reaction is diluted with water (400 mL) and extracted with EtOAc (400 mL). The organic layer is washed with water (2 x 400 mL), dried over Na_2SO_4 and concentrated. The product is then purified by CombiFlash® Companion in two batches to provide allyl ether **14b** (12g, 92% yield).

Step 2:

A solution of n-BuLi in hexanes (2.5 M, 6.4 mL, 16 mmol) is added dropwise to a precooled (-78°C) suspension of methyltriphenylphosphonium bromide (6.6 g, 19 mmol) in THF (90 mL). The resulting bright yellow mixture is stirred for 5 min at -78°C, warmed to RT over approximately 5 min and then recooled to -78°C. Aldehyde **14b** (2.4 g, 14 mmol) dissolved in THF (10 mL) is added dropwise and the reaction is allowed to proceed for 10 min at -78°C before being allowed to warm to RT and stir overnight. The reaction is quenched with brine (100 mL), diluted with

water (100 mL) and extracted with EtOAc (100 mL). The organic layer is then washed with water (2 x 100 mL), dried over Na_2SO_4 and concentrated. The crude yellow liquid is then taken up in EtOAc (1 mL) and diluted with hexanes (20 mL), after which Ph_3PO precipitates as a white solid. The solid is removed by filtration, washed with 1:9 EtOAc:hexanes (50 mL) and the filtrates are evaporated to dryness. The product is purified by CombiFlash® Companion to give diene **14c** (1.3 g, 54% yield).

Step 3:

Grubb's second generation catalyst (50 mg, 0.075 mmol) is added to a degassed solution of diene **14c** (1.3 g, 7.5 mmol). After stirring under Ar for 2.5 h, the reaction is concentrated onto SiO_2 (about 2 g) and the product purified by CombiFlash® Companion to give benzopyran **14d** (940 mg, 86% yield) as a clear oil.

Step 4:

Solid Pd-C (10% w/w, 680 mg, 0.64 mmol) is added to a solution of benzopyran **14d** (940 mg, 6.4 mmol) in EtOH (8.5 mL) and the flask is evacuated and backfilled with H_2 gas (balloon). After stirring the reaction at RT for 2.5 h, the mixture is filtered through Celite® (EtOAc washing) and then the filtrate is concentrated to dryness. The product is purifed by CombiFlash® Companion to provide chroman **14e** (800 mg, 84% yield).

Step 5:

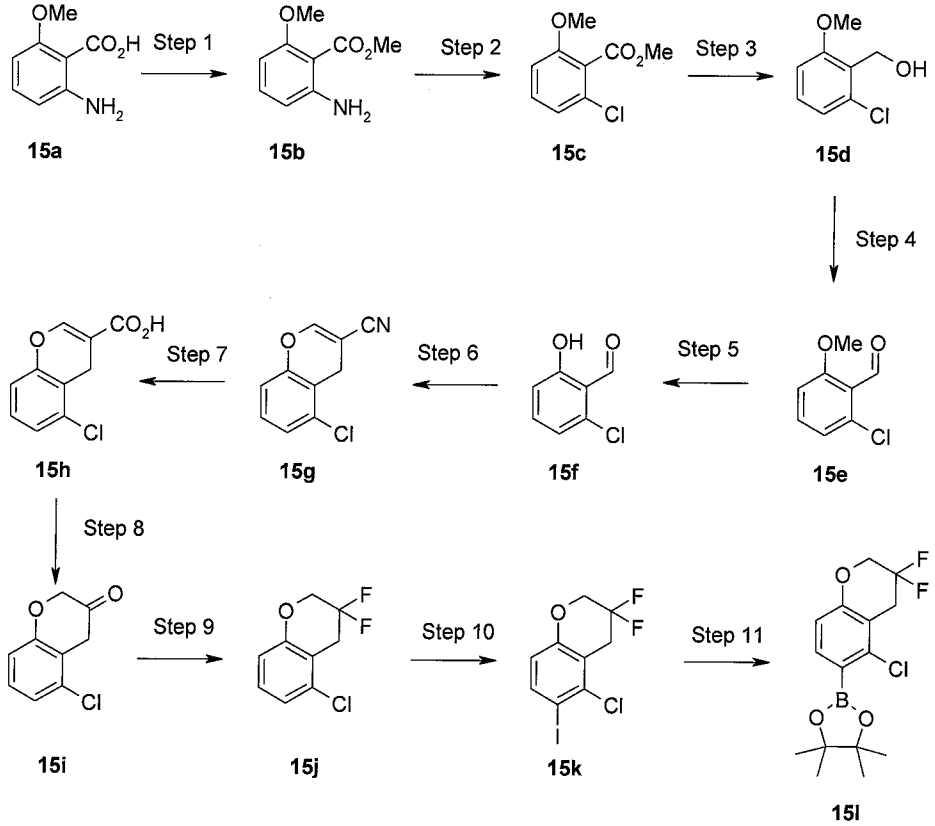
Neat Br_2 (275 µL, 5.4 mmol) is added dropwise to a solution of chroman **14e** (800 mg, 5.4 mmol) dissolved in AcOH (25 mL). The reaction is then diluted with water (50 mL) and EtOAc (50 mL). The organic layer is washed with water (2 x 50 mL) and saturated $NaHCO_3$ (2 x 50 mL). The organic layer is dried over Na_2SO_4 and concentrated to dryness. The product is purified by CombiFlash® Companion to give bromide **14f** as a mixture with the dibromide (1.3 g, 68% by mass **14f**, 51% yield).

Step 6:

A solution of the bromide **14f** (950 mg, 2.8 mmol), bis[pinocolato]diborane (840 mg, 3.3 mmol) and potassium acetate (920 g, 9.6 mmol) in DMF (30 mL) is degassed with Ar for 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (290 mg,

0.36 mmol). The reaction mixture is then degassed for an additional 5 min before being heated to 95°C for 3 h. The reaction is then cooled to RT. The crude reaction mixture is diluted with water and the product is extracted 3 times with EtOAc (3 x 20 mL). The combined organics are washed with water (2 x 20 mL). The organic phase is then dried over Na_2SO_4, filtered and concentrated. The crude mixture is further purified by CombiFlash® Companion to afford boronic ester **14g** (403 mg, 53% yield) as a pale yellow solid.

Example 15: Synthesis of boronate fragment **15l**



Step 1:

An ethereal solution of diazomethane (0.7 M, 100 mL) is added to a solution of **15a** (5.0 g, 30 mmol) in ether (20 mL). After consumption of the SM (TLC monitoring), the reaction is concentrated onto SiO_2 (about 10 g) and the product purified by CombiFlash® Companion to yield ester **15b** (5.2 g, 95% yield).

Step 2:

A solution of $NaNO_2$ (2.1 g, 30 mmol) in water (10 mL) is slowly added to a solution

of aniline **15b** (5.0 g, 28 mmol) dissolved in AcOH (50 mL) and 2 M HCl (75 mL) at 0°C. The resulting mixture is stirred at this temperature for 1 h. Solid CuCl (8.4 g, 85 mmol) is added portionwise (over 2 min). The reaction is allowed to come to RT, is stirred for 30 min and then is warmed to 60°C for 40 min. The mixture is poured into water (200 mL) and extracted with EtOAc (2 x 200 mL). The organic layer is dried with $MgSO_4$, filtered and evaporated to dryness. The product is purified by CombiFlash® Companion to afford aryl chloride **15c** (3.8 g, 68% yield).

Step 3:

A solution of DIBAL in DCM (1 M, 42 mL, 42 mmol) is added dropwise over a period of 25 min to a precooled (-78°C) solution of ester **15c** (3.8 g, 19 mmol) in dry CH_2Cl_2 (100 mL). The reaction is allowed to stir for 2 h at -78°C. The reaction is quenched at -78°C by the dropwise addition of 1 N HCl (8 mL). The reaction is allowed to warm to RT and the organic phase washed with a 5% solution of Rochelle's salt (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude benzyl alcohol **15d** (3.2 g, 99% yield), which is used in the next step without any further purification.

Step 4:

Solid Dess Martin reagent (8.7 g, 20 mmol) is added to a precooled (0°C) solution of alcohol **15d** in dry CH_2Cl_2 (100 mL). The reaction is allowed to stir for 2 h while slowly warming to RT. At this time, another 0.5 g of Dess Martin Periodinane is added and the reaction continues for another 1 h. A 1:1 mixture of saturated $NaHCO_3$ and 0.5 M $Na_2S_2O_3$ (100 mL) is added and this mixture is stirred vigorously until the phases become clear (approximately 30 min). The organic phase is separated and the aqueous phase is extracted with DCM (100 mL) and washed with saturated $NaHCO_3$ (100mL). The combined organic phases are then dried over $MgSO_4$ and evaporated. The product is purified by CombiFlash® Companion to give aldehyde **15e** (2.9 g, 90% yield).

Step 5:

A solution of methyl ether **15e** (720 mg, 4.2 mmol) in anhydrous CH_2Cl_2 (20 mL) is added slowly to a precooled (-30 °C) solution of BBr_3 (1 M, 8.4 mL, 8.4 mmol). The solution is warmed to 0°C and is stirred for 3 h. The reaction is quenched carefully with methanol (1 mL) and washed with saturated $NaHCO_3$ and then brine (25 mL

each). The organic layer is dried over $MgSO_4$, filtered and concentrated and the product is purified by CombiFlash® Companion to give phenol **15f** (530 mg, 80% yield).

Step 6:

A mixture of the aldehyde **15f** (1.1 g, 7.2 mmol), acrylonitrile (2.4 mL, 36 mmol) and DABCO (190 mg, 1.7 mmol) are refluxed for 5 h. The reaction mixture is cooled to RT, diluted with EtOAc (50 mL) and washed with 1 N NaOH (20 mL) and then with 1 N HCl (20 mL). The organic phase is dried over $MgSO_4$ and concentrated to dryness. The product is purified by CombiFlash® Companion to afford the nitrile **15g** (650 mg, 47% yield).

Step 7:

A mixture of nitrile **15g** (650 mg, 3.4 mmol), 10% NaOH (10 mL, 25 mmol) and EtOH (95%, 0.5 mL) is heated to reflux for 5 days. The reaction is then cooled to RT and 1 N HCl is then added until pH 4. The precipitate is then collected by filtration, washed with water and dried *in vacuo* to give acid **15h** (740 mg, >99% yield).

Step 8:

Triethylamine (0.56 mL, 4.0 mmol) and diphenylphosphoryl azide (0.75 mL, 3.5 mmol) are added successively to a solution of acid **15h** (714 mg, 3.4 mmol) in dry toluene (40 mL). This mixture is heated to 85°C for 2 h and then cooled to RT and treated with 6 N HCl (6 mL). The mixture is brought to reflux and is stirred at this temperature for 2 h. The reaction is then cooled to RT, diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2 x 100 mL), water (2 x 100 mL) and brine (100 mL). The organic layer is dried over $MgSO_4$, filtered and evaporated to dryness. The product is then purified by CombiFlash® Companion to give ketone **15i** (269 mg, 44% yield).

Step 9:

Deoxofluor® (0.54 mL, 2.9 mmol) is added to a solution of ketone **15i** (270 mg, 1.5 mmol) in CH_2Cl_2 (0.6 mL) and EtOH (17 µL) in a sealed tube. The sealed tube is heated to 40°C for 24 h. The tube is then unsealed, cooled to 0°C and the reaction quenched by the **slow** (Exothermic) addition of saturated $NaHCO_3$ (1 mL). The crude reaction mixture is diluted with water (20 mL) and extracted with DCM (3 x 20

mL). The combined organics are washed with water (20 mL) and the organic phase is dried over $MgSO_4$, filtered and concentrated. The product is purified by CombiFlash® Companion to provide difluorochroman **15j** (225 mg, 71% yield).

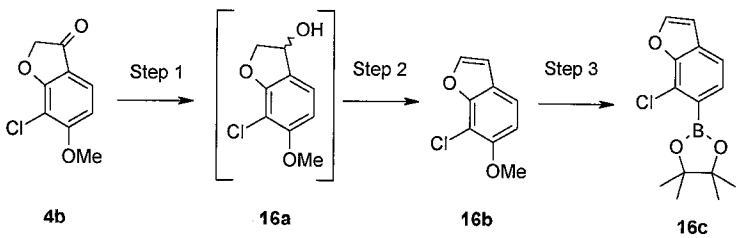
Step 10:

Solid silver nitrate (187 mg, 1.1 mmol) and iodine (279 mg, 1.1 mmol) are added successively to a solution of difluorochroman **15j** (225 mg, 1.1 mmol) dissolved in MeOH (7.8 mL). The reaction is stirred at RT for 90 min and then filtered through a pad of Celite®. The filtrate is treated with a drop of 0.5 N $Na_2S_2O_3$ (orange color dissipated) then concentrated under reduced pressure. The residue is partitioned between H_2O, 0.5N $Na_2S_2O_3$ and EtOAc (20 mL each). The water layer is extracted with EtOAc (3 x 20 mL) and the combined organics are washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The product is purified by CombiFlash® Companion to give aryl iodide **15k** (158 mg, 44% yield).

Step 11:

A solution of the aryl iodide **15k** (150 mg, 0.45 mmol), bis[pinocolato]diborane (150 mg, 0.59 mmol) and potassium acetate (130 mg, 1.4 mmol) in DMF (5 mL) is degassed with Ar for 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (44 mg, 0.054 mmol). The reaction mixture is then degassed for an additional 5 min before being heated to 85°C for 9 h. The reaction is then cooled to RT. The crude reaction mixture is diluted with water and the product is extracted with EtOAc (3 x 10 mL). The combined organics are washed with water (10 mL) and brine (10 mL). The organic phase is then dried over $MgSO_4$ and filtered and concentrated. The crude mixture is further purified by CombiFlash® Companion to afford boronic ester **15l** (123 mg, 70% pure by NMR, 57% yield).

Example 16: Synthesis of boronate fragment **16c**



4b **16a** **16b** **16c**

Step 1:

Solid $NaBH_4$ (342 mg, 9.0 mmol) is added to a solution of ketone **4b** (1.5 g, 7.5 mmol) dissolved in MeOH (10 mL) and THF (25 mL) at 0°C is then added. The reaction is warmed to RT and is allowed to stir for 1 h. The reaction is quenched with aqueous HCl (1 N, 5 mL), the MeOH is removed by concentration and the product extracted with EtOAc (2 x 50 mL). The organic layer is washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to afford alcohol **16a** (1.52 g >99% yield). This material is used as is in the next step.

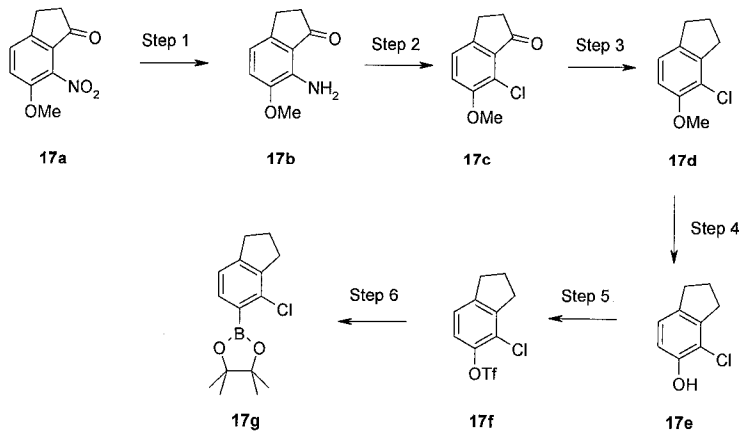
Step 2:

TFA (2.9 mL) is added dropwise to a solution of crude alcohol **16a** (1.5 g; 7.47 mmol) in DCM (28 mL) at 0°C. The solution is stirred for 30 min, then concentrated to dryness. The residue is taken up in EtOAc, washed with $NaHCO_3$ (saturated), brine, dried over Na_2SO_4, filtered and concentrated to a pale yellow gum. The product is purified by CombiFlash® Companion to afford benzofuran **16b** (0.30 g, 22% yield) as a white solid.

Step 3:

Compound **16c** is prepared from **16b** following a synthetic sequence identical to steps 3 to 5 of Example 4.

Example 17: Synthesis of boronate fragment **17g**



Step 1:

Zn dust (7.89 g, 121 mmol) is added to a solution of **17a** (5.0 g, 24 mmol) in AcOH (100 mL). The reaction mixture is then heated to 100°C and is stirred overnight. The reaction is cooled to RT and the mixture is filtered (EtOAc washing), the solvent is

evaporated and the residue purified by CombiFlash® Companion (30% EtOAc/hexanes) to afford aniline **17b** (3.06 g, 72% yield) as a yellow solid.

Step 2:

A solution of $NaNO_2$ (640 mg, 9.3 mmol) in water (3 mL) is slowly added to a solution of aniline **17b** (1.5 g, 8.5 mmol) dissolved in AcOH (12 mL) and 2 M HCl (25 mL) at 0°C. The resulting mixture is stirred at this temperature for 1 h. Solid CuCl (2.6 g, 26 mmol) is added portionwise (over 2 min) and the reaction is allowed to come to RT, is then stirred for 30 min and then is warmed to 60°C for 40 min. The mixture is poured into water (100 mL) and extracted with EtOAc (2 x 100 mL). The organic layer is dried with $MgSO_4$, filtered and evaporated to dryness. The product is purified by CombiFlash® Companion (40% EtOAc/hexanes) to afford aryl chloride **17c** (1.11 g, 99% yield) as a pale yellow solid.

Step 3:

Solid pre-activated Zn dust is added to a solution of ketone **17c** in AcOH. The reaction mixture is then heated to 100°C and stirred at that temperature for 4 h. The reaction mixture is filtered (EtOAc washing), the filtrate is evaporated to dryness and the product purified by CombiFlash® Companion (10% EtOAc/hexanes) to afford indane **17d** (902 mg, 88% yield) as a white crystalline solid.

Step 4:

A solution of BBr_3 in DCM (1 M, 9.9 mL, 9.9 mmol) is added dropwise to a precooled (-78°C) solution of methyl ether **17d** (902 mg, 4.9 mmol) dissolved in DCM (20 mL). The reaction solution is stirred at this temperature for 10 min and allowed to warm to RT. After stirring for 1.5h, water (50 mL) is added (Exothermic) and the mixture is extracted with DCM (3 x 50 mL). The combined organic layers are dried over $MgSO_4$, filtered and evaporated to dryness. The product is purified by CombiFlash® Companion to afford phenol **17e** (700 mg, 84% yield) as an off-white solid.

Step 5:

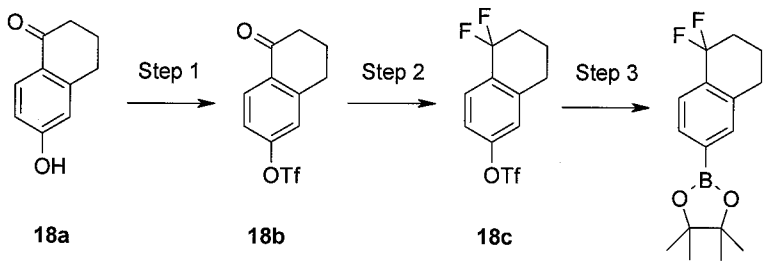
Tf_2O (1.05 mL, 12 mmol) is added to a precooled (0°C) solution of phenol **17e** (700 mg, 4.1 mmol) and Et_3N (1.7 mL, 12 mmol) in DCM (20 mL). The resulting dark solution is allowed to warm to RT. After 25 min, the reaction is quenched with saturated $NaHCO_3$ (10 mL), diluted with DCM, and the organic layer washed with

water, brine, dried over $MgSO_4$ and evaporated to dryness. The product is purified by CombiFlash® Companion (10% EtOAc/hexanes) to afford triflate **17f** (1.21 g, 97% yield) as a yellow oil.

Step 6:

A solution of triflate **17f** (1.2 g, 4.0 mmol), bis[pinocolato]diborane (1.5 g, 6.0 mmol) and potassium acetate (1.3 g, 14 mmol) in DMF (20 mL) is degassed with Ar for 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (490 mg, 0.60 mmol). The reaction mixture is then degassed for an additional 5 min before being heated to 95°C for 5 h. The reaction is then cooled to RT. The crude reaction mixture is diluted with water and the product is extracted with EtOAc (3 x 100 mL). The combined organics are washed with water (100 mL) and brine (100 mL). The organic phase is then dried over $MgSO_4$ and filtered and concentrated. The crude mixture is further purified by CombiFlash® Companion (10 % EtOAc/hexanes) to afford boronic ester **17g** (593 mg, 53% yield) as a pale yellow solid.

Example 18: Synthesis of boronate fragment **18d**



18a **18b** **18c** **18d**

Step 1:

Neat Tf_2O (0.83 mL, 4.9 mmol) is added dropwise to a cooled (0°C) solution of phenol **18a** (0.50 g, 3.1 mmol) and pyridine (1.3 mL, 17 mmol) in DCM (15 mL). The reaction is allowed to warm to RT and stir overnight. The reaction is quenched by the addition of a 10% citric acid solution (50 mL) and the mixture is extracted with DCM (3 x 50 mL). The combined organics are washed with water (50 mL), dried over $MgSO_4$, filtered and concentrated. The product is purified by CombiFlash® Companion to give triflate **18b** (500 mg, 94% yield).

Step 2:

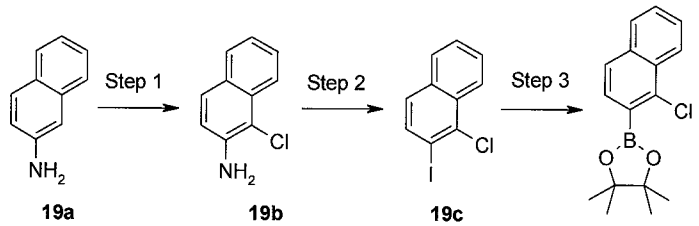
Deoxyfluor® (0.83 mL, 4.2 mmol) followed by EtOH (10 uL, 0.2 mmol) are added to

neat triflate **18b** (500 mg, 1.7 mmol) in a sealable tube. The tube is sealed and the reaction is heated in an oil bath at 85°C and is stirred overnight. The reaction is then cooled to 0°C and quenched by the slow addition of $NaHCO_3$ (100 µL, Exothermic). The mixture is diluted with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers are washed with water (50 mL) and brine (50 mL). The organic phase is then dried over $MgSO_4$, filtered and concentrated. The crude product is purified by CombiFlash® Companion to provide the difluorotetrahydronaphtyl triflate **18c** (175 mg, 33% yield).

Step 3:

Step three is performed exactly as in step 6 of Example 17 to provide boronic ester **18d**.

Example 19: Synthesis of boronate fragment **19d**



Step 1:

Solid N-chlorosuccinimide (2.2 g, 16 mmol) is added in portions over 5 min to a solution of naphthylamine **19a** (2.3 g, 16 mmol) dissolved in CCl_4 (150 mL). The reaction is then heated to 50°C and is stirred for 40 min. The reaction is then cooled to RT, solids are removed by filtration and the filtrate is washed with water (100 mL), dried over $MgSO_4$ and evaporated to dryness to provide chloroaniline **19b** (2.8 g, 96% yield).

Step 2:

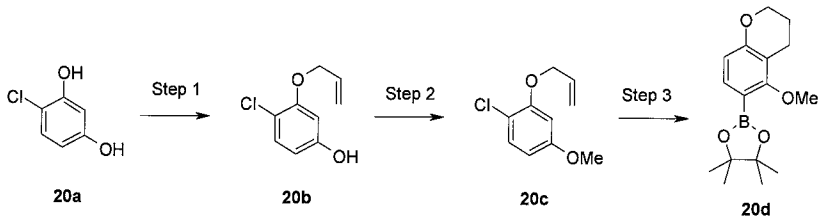
A solution of $NaNO_2$ (1.2 g, 17 mmol) in water (5 mL) is slowly added to a precooled (0°C) suspension of aniline **19b** (2.8 g, 15 mmol) in 12 N HCl (7 mL) and ice (9.7 g), so as to maintain the temperature below 5°C. The mixture is stirred for 15 min and then is transferred to a solution of KI (8.7 g, 52 mmol) in water (30 mL) and the resulting mixture is stirred for 2 h. The mixture is extracted with Et_2O (3 x 100 mL)

and the combined organic layers washed successively with 3 N NaOH (2 x 50 mL), 5% $NaHSO_3$ (50 mL) and brine (100 mL). The organic phase is dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is purified by flash chromatography (EtOAc/hexanes) to provide aryl iodide **19c** (2.4 g, 54% yield).

Step 3:

Step three is carried out exactly as described in step 11 of Example 15 to provide boronic ester **19d**.

Example 20: Synthesis of boronate fragment **20d**



20a 20b 20c 20d

Step 1:

Allyl bromide (2.1 mL, 25 mmol) followed by potassium carbonate (7.2 g, 52 mmol) are added to a solution of 6-chlororesorcinol **20a** (10 g, 69 mmol) dissolved in DMF (120 mL). The reaction is stirred overnight, diluted with EtOAc (500 mL) and washed with water (3 x 500 mL). The organic layer is dried over $MgSO_4$ and concentrated to dryness. The crude product is purified by CombiFlash® Companion to obtain allyl ether **20b** (1.8g, 40% yield).

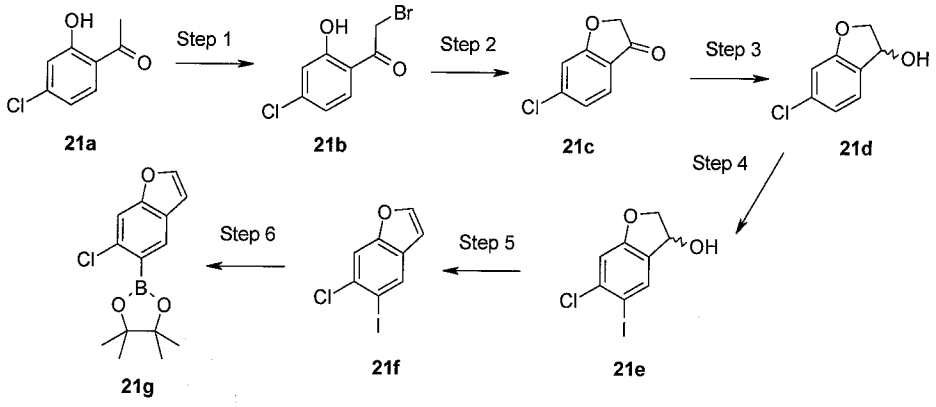
Step 2:

Methyl iodide (1.2 mL, 20 mmol) followed by potassium carbonate (3.8 g, 27 mmol) are added to a solution of phenol **20b** (1.8 g, 9.8 mmol) dissolved in DMF (12 mL). The reaction is stirred for 2 h, diluted with EtOAc (50 mL) and washed with water (3 x 50 mL). The organic layer is dried over $MgSO_4$ and concentrated to dryness. The crude product is purified by CombiFlash® Companion to obtain methyl ether **20c** (1.8g, 40% yield).

Step 3:

Step 3 is comprised of a sequence of steps identical to steps 2 through 6 of Example 12, followed by step 1 of Example 13 to provide boronic ester **20d**.

Example 21: Synthesis of boronate fragment **21g**



Step 1:

Solid $CuBr_2$ (7.9 g; 35 mmol) is added to a solution of **21a** (4.0 g, 23 mmol) dissolved in EtOAc (32 mL) and $CHCl_3$ (32 mL). The mixture is heated to reflux and is stirred for 8 h. $CuBr_2$ (3.9 g) is then added and the mixture continues to stir at reflux for an additional 15 h. The mixture is cooled to RT, the solids removed by filtration (EtOAc washing). The filtrate is concentrated to afford the crude bromoketone **21b** (6.3 g), which is used directly in the next step.

Step 2:

Solid KF (2.5 g, 43 mmol) is added to a solution of crude bromoketone **21b** (6.3 g, 23 mmol) dissolved in DMF (21 mL). The reaction is stirred at RT for 3 h and then taken up in ether (300 mL), washed with brine (3 x 100 mL), dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is purified by CombiFlash® Companion to afford ether **21c** (2.1 g, 49% yield over two steps).

Step 3:

Solid $NaBH_4$ (270 mg, 7.1 mmol) is added to a precooled (0°C) solution of ketone **21c** (1.0 g, 5.9 mmol) dissolved in MeOH (20 mL). The reaction is allowed to stir for 1 h and then quenched with aqueous HCl (1 N, 1 mL). The volatiles are removed *in vacuo* and the product extracted with EtOAc (20 mL). The organic layer is washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated to afford the crude alcohol **21d** (1.0 g), which is used directly in the next step.

Step 4:

Solid $AgNO_3$ (1.0 g, 6.1 mmol) followed by I_2 (1.6 g, 6.2 mmol) are added to a solution of alcohol **21d** (1.0 g, 6.2 mmol) dissolved in MeOH (58 mL). The mixture is stirred at RT for 1 h and then a solution of $Na_2S_2O_4$ (0.5 M, 10 mL) is added and the mixture is stirred for 30 min. The MeOH is removed *in vacuo* and the residue taken up in EtOAc (50 mL), washed with water (1 x 50 mL), brine (1 x 50 mL), dried (Na_2SO_4), filtered and concentrated to afford aryl iodide **21e** (1.6 g), which is used directly in the next step.

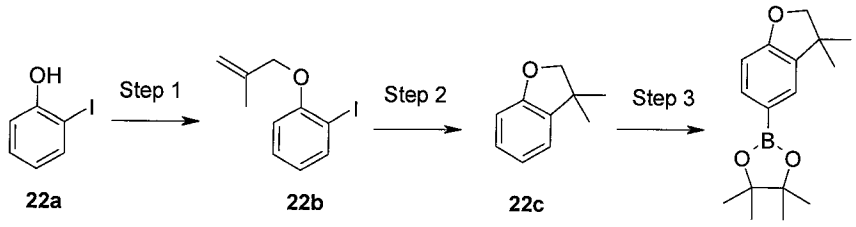
Step 5:

Crude alcohol **21e** (1.6 g, 5 mmol) is dissolved in a mixture of DCM (20 mL) and TFA (2.2 mL). The reaction is stirred for 45 min and then concentrated to dryness. The residue is taken up in EtOAc (50 mL), washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer is dried over Na_2SO_4, filtered and concentrated to dryness. The crude product is purified by CombiFlash® Companion to provide benzofuran **21f** (978 mg, 65% yield over 3 steps).

Step 6:

Step 6 is carried out exactly as described for step 11 of Example 15 to provide boronic ester **21g**.

Example 22: Synthesis of boronate fragment **22d**



22a 22b 22c 22d

Step 1:

Neat 3-bromo-2-methylpropene (1.7 mL, 16 mmol) is added to a suspension of phenol **22a** (3.0 g, 14 mmol) and potassium carbonate (5.6 g, 41 mmol) in DMF (35 mL). The reaction is stirred for 2 h and then quenched with water (100 mL) and extracted with hexanes (2 x 100 mL). The organic phase is washed with brine (2 x 100 mL) and concentrated to give ether **22b** (3.3 g, 87% yield).

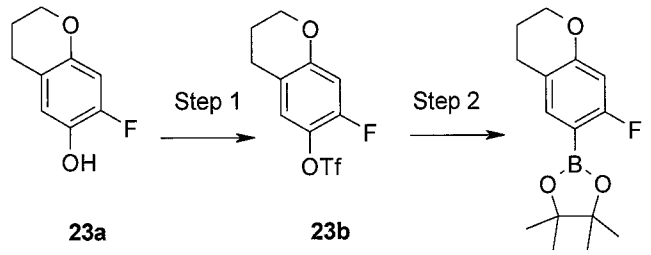
Step 2:

Neat tributyltin hydride (2.3 mL, 8.8 mmol) is added to a solution of aryliodide **22b** (2.0 g, 7.3 mmol) and AIBN (120 mg, 0.73 mmol) in PhMe (40 mL) and the reaction is then stirred at reflux under N_2. After 1 h, the reaction is concentrated to dryness and the crude product purified by CombiFlash® Companion to provide dihydrobenzofuran **22c** (785 mg, 73% yield).

Step 3:

Step 3 is comprised of a sequence of synthetic steps identical to steps 10 and 11 of Example 15 to provide boronic ester **22d**.

Example 23: Synthesis of boronate fragment **23c**



23a **23b** **23c**

Step 1:

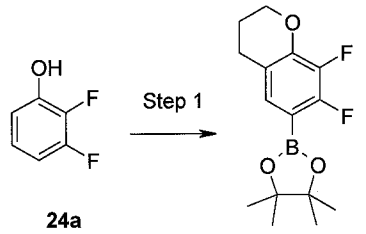
Neat Tf_2O (0.56 mL, 3.3 mmol) is added dropwise to a cooled (0°C) solution of phenol **23a** (350 mg, 2.1 mmol; prepared according to Doi *et al Bull. Chem. Soc. Jpn.* **2004** 77, 2257-2263) and pyridine (0.91 mL, 11 mmol) in DCM (10 mL) under an Ar atmosphere. The reaction is allowed to warm to RT and then is stirred for 2 h. The reaction is quenched by the addition of a 10% citric acid solution (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layers are washed with water (20 mL), dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is purified by CombiFlash® Companion to provide triflate **23b** (512 mg, 82% yield).

Step 2:

A solution of the triflate **23b** (510mg, 1.7 mmol), bis[pinocolato]diborane (560 mg, 2.2 mmol) and potassium acetate (500 mg, 5.1 mmol) in DMF (18 mL) is degassed with Ar for 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (140 mg, 0.17 mmol). The reaction mixture is then degassed for an additional 5 min before

being heated to 100°C by microwave irradiation for 10 min. The reaction is then cooled to RT. The crude reaction mixture is diluted with EtOAc (60 mL) and washed with brine (3 x 60 mL). The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude mixture is further purified by CombiFlash® Companion to afford boronic ester **23c** (200 mg, 42% yield).

Example 24: Synthesis of boronate fragment **24b**

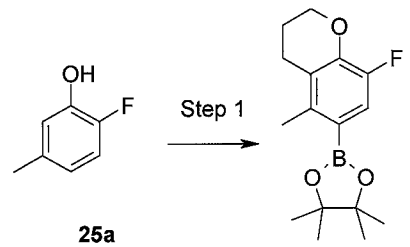


24a **24b**

Step 1:

Compound **24b** is prepared from **24a** following a synthetic sequence identical to steps 1 to 6 of Example 12.

Example 25: Synthesis of boronate fragment **25b**

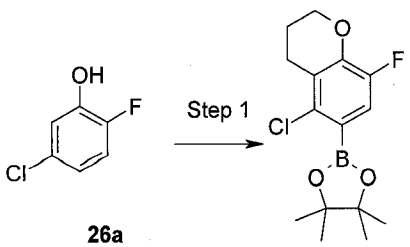


25a **25b**

Step 1:

Compound **25b** is prepared from **25a** following a synthetic sequence identical to steps 1 to 6 of Example 12.

Example 26: Synthesis of boronate fragment **26b**

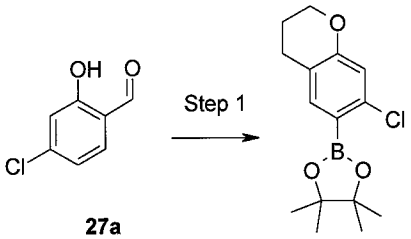


26a **26b**

Step 1:

Compound **26b** is prepared from **26a** following a synthetic sequence identical to steps 1 to 6 of Example 12.

Example 27: Synthesis of boronate fragment **27b**

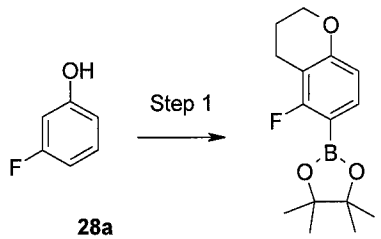


27a **27b**

Step 1:

Compound **27b** is prepared from **27a** following a synthetic sequence identical to steps 1 to 6 of Example 14.

Example 28: Synthesis of boronate fragment **28b**

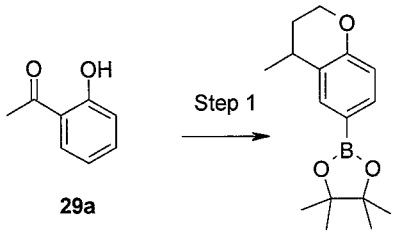


28a **28b**

Step 1:

Compound **28b** is prepared from **28a** following a synthetic sequence identical to steps 1 to 8 of Example 6.

Example 29: Synthesis of boronate fragment **29b**

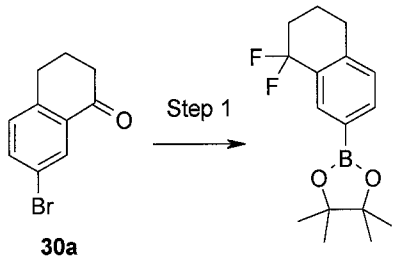


29a 29b

Step 1:

Compound **29b** is prepared from **29a** following a synthetic sequence identical to steps 1 to 6 of Example 14.

Example 30: Synthesis of boronate fragment **30b**

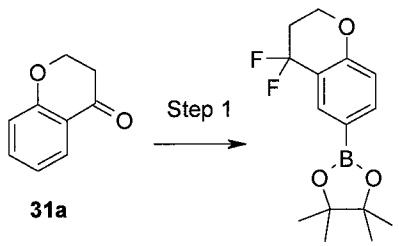


30a 30b

Step 1:

Compound **30b** is prepared from **30a** following a synthetic sequence identical to steps 2 and 3 of Example 18.

Example 31: Synthesis of boronate fragment **31b**

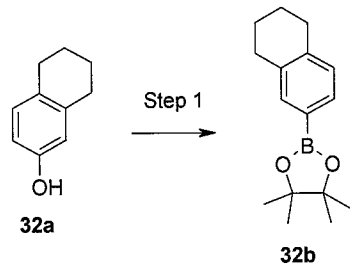


31a 31b

Step 1:

Compound **31b** is prepared from **31a** following a synthetic sequence identical to steps 9 to 11 of Example 15.

Example 32: Synthesis of boronate fragment **32b**

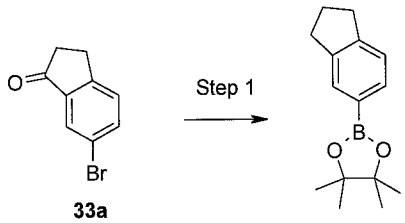


32a **32b**

Step 1:

Compound **32b** is prepared from **32a** following a synthetic sequence identical to steps 5 to 6 of Example 17.

Example 33: Synthesis of boronate fragment **33b**

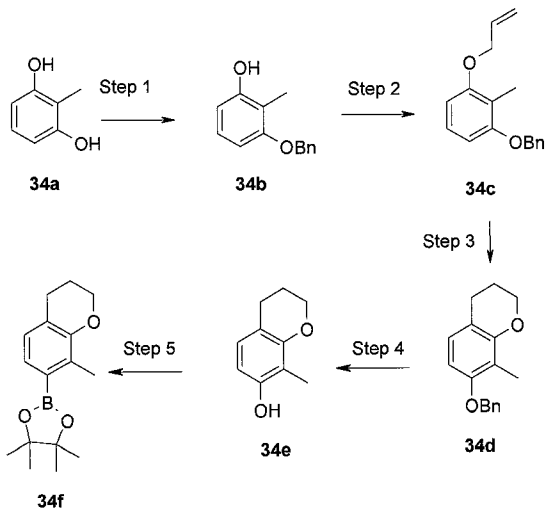


33a **33b**

Step 1:

Compound **33b** is prepared from **33a** following a synthetic sequence identical to steps 1 and 4 of Example 11.

Example 34: Synthesis of boronate fragment **34f**



34a **34b** **34c** **34d** **34e** **34f**

Step 1:

Benzyl bromide (25 mL, 210 mmol) followed by potassium carbonate (44 g, 320 mmol) are added to a solution of 2-methylresorcinol **34a** (38 g, 310 mmol) dissolved in DMF (1 L). The reaction is stirred overnight, diluted with EtOAc (2 L) and washed with water (3 x 2 L). The organic layer is dried over Na_2SO_4 and concentrated to dryness. The crude product is purified by CombiFlash® Companion to obtain benzyl ether **34b** (18.6 g, 39% yield).

Step 2:

Allyl bromide (3.0 mL, 35 mmol) followed by potassium carbonate (6.5 g, 47 mmol) are added to a solution of phenol **34b** (5 g, 23 mmol) dissolved in DMF (100 mL). The reaction is stirred overnight, diluted with EtOAc (500 mL) and washed with water (3 x 500 mL). The organic layer is dried over Na_2SO_4 and concentrated to dryness. The crude product is purified by CombiFlash® Companion to obtain benzyl ether **34c** (4.4 g, 75% yield).

Step 3:

Compound **34d** is prepared from **34c** following a synthetic sequence identical to steps 2 to 4 of Example 12.

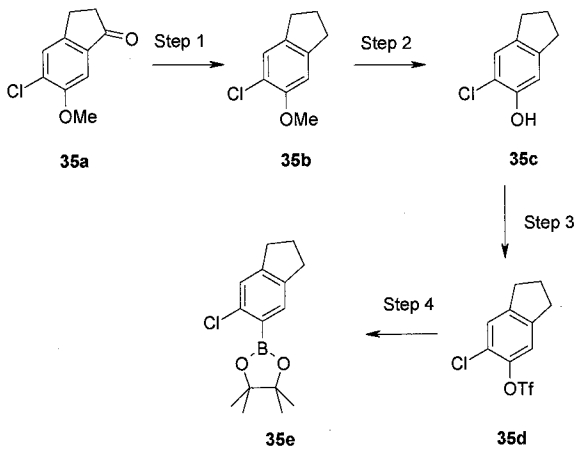
Step 4:

Benzyl ether **34d** and Pd-C (10% w/w, 100 mg, 0.094 mmol) are combined in EtOAc (5 mL) and the flask is evacuated and backfilled with a H_2 atmosphere (balloon). After stirring for 3 h, the reaction is filtered through Celite® (EtOAc washing) and the filtrated concentrated to give phenol **34e** (145 mg, 95% yield).

Step 5:

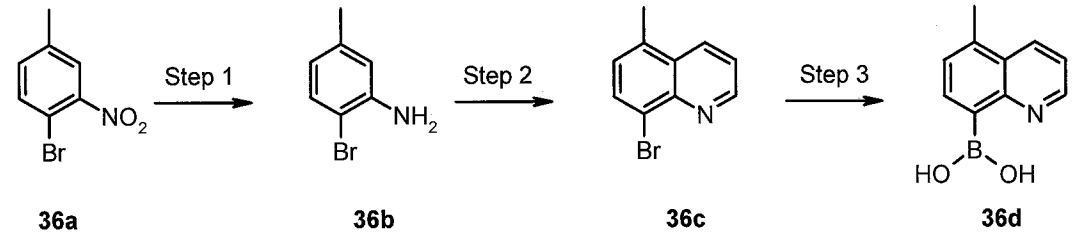
Compound **34f** is prepared from **34e** following a synthetic sequence identical to steps 5 to 6 of Example 17.

Example 35: Synthesis of boronate fragment **35e**



Steps 1 through 4 are done in analogy to steps 3 through 6 from Example 17.

Example 36: Synthesis of boronate fragment **36d**



Step 1:

4-bromo-3-nitrotoluene **36a** (5.0 g, 22.9 mmol) is dissolved in 50 mL ethyl acetate and solid tin(II) chloride dihydrate (20.0 g, 86.9 mmol) is added. The mixture is heated under nitrogen atmosphere at 70°C for 2 h (note: temporary overheating to 100°C is observed! Caution should be exercised!). The mixture is cooled down and is poured into 200 mL of ice-water. 5% aqueous $NaHCO_3$ (50 mL) solution is added (rapid foaming!), followed by 10 N aqueous NaOH to bring the pH ~ 7-8. Large volume of gelatinous yellowish precipitate is formed. This heterogeneous mixture is shaken with EtOAc (200 mL) and the mixture is centrifuged in 50 mL portions, resulting in good separation of a yellowish solid. The clear supernatant is decanted and is extracted with EtOAc. Combined organic phase is washed with brine, dried over sodium sulphate, filtered and concentrated under vacuum to give an orange oily residue. This residue is re-dissolved in 100 mL of ether and the solution is washed with 10% Na_2CO_3 (20 mL) followed by 2.5 M aqueous NaOH (20 mL). The dark brown organic solution is then stirred with $MgSO_4$ and active charcoal and filtered to give a light yellow solution, which darkened rapidly on standing in open flask. The

solvent is removed under vacuum to give the desired compound **36b** as a brown-red oil which is used in the next step without further purification (3.31 g, 78% yield).

Step 2:

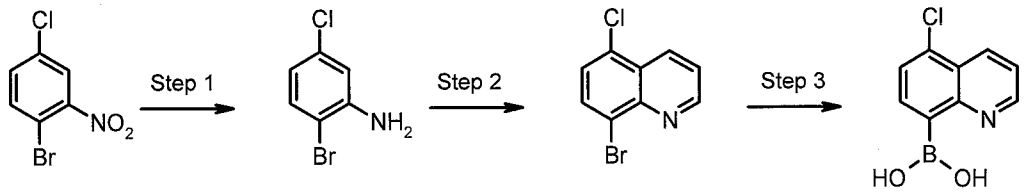
A mixture of compound **36b** (3.3 g, 17.7 mmol), glycerin (3.3 g, 35.5 mmol), nitrobenzene (2.2 g, 17.7 mmol) and 75% aqueous sulfuric acid (10 mL, 138 mmol) is stirred at 150°C for 3 h (mixture turns black and viscous). The reaction mixture is cooled down, poured into ice-water (200 mL) and 10 N aqueous NaOH is added (30 mL, 300 mmol). The black mixture is then shaken with EtOAc (100 mL) and is centrifuged in 50 mL portions. The upper EtOAc layers are combined and the bottom aqueous layers containing the black tar are shaken with EtOAc and re-centrifuged. All EtOAc extracts are combined, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum to give a brown-red oil. This material is chromatographed on 80 g silica gel column (CombiFlash® Companion apparatus, hexane-EtOAc gradient). The fractions containing the compound are concentrated under vacuum to afford compound **36c** as a white solid (3.26 g, 83% yield).

Step 3:

To a cooled (-78 °C) solution of compound **36c** (500 mg, 2.25 mmole) in anhydrous Et_2O (20 mL), is added over 5 min under an Ar atmosphere a 1.6 M solution of *n*-BuLi in hexane (3.5 mL, 5.60 mmol). The mixture is stirred at -78 °C for 50 min, triisopropylborate (2.00 mL, 8.55 mmol) is then added dropwise and the mixture is stirred for 2 h at that temperature. The mixture is slowly allowed to reach RT over a 2 h period and it is poured into 1 M aqueous HCl (30 mL). The mixture is transferred into a separatory funnel, the organic layer is separated and the aqueous layer is washed with Et_2O. The aqueous layer is then transferred into a 500 mL Erlenmeyer flask and the pH of the solution is adjusted to 6.3 (measured with a pH meter) by slowly adding a saturated solution of $NaHCO_3$ in water (~25 mL, careful: foaming). The suspension is filtered off and the separated light-beige solid is washed with water and dried under high vacuum. This crude product (383 mg) is triturated with Et_2O /hexanes to give a first crop of the desired compound **36d** as a free base (120 mg, 28% yield). The mother liquors are concentrated under vacuum and are purified by reversed-phase HPLC using a CH_3CN/H_2O gradient containing 0.06% TFA (ODS-AQ, C-18 column, 75 x 30 mm, 5-µm particle size). After lyophilization, a second crop of compound **36d** is obtained as a TFA salt (102 mg, 15% yield), (total yield:

43%).

Example 37: Synthesis of boronate fragment **37d**



37a **37b** **37c** **37d**

Step 1:

1-bromo-4-chloro-2-nitrobenzene **37a** is transformed to compound **37b** using the procedure of example **36b**, except for the fact that Et_2O is used for the extractions instead of EtOAc.

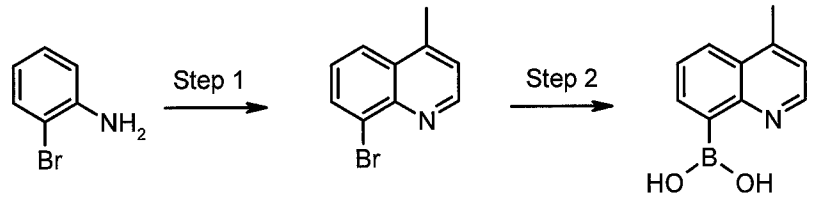
Step 2:

Compound **37b** (4.2 g, 20.3 mmol) is melted at 50°C in a 100 mL round-bottomed flask containing a stirring bar and immersed in an oil bath. A solution of zinc chloride (700 mg, 5.03 mmol) and ferric chloride (540 mg, 3.25 mmol) in water (3.3 mL) is added in one portion followed by absolute EtOH (20 mL). The flask is stoppered with a rubber septa and a needle is inserted to avoid any pressure build-up. The mixture is warmed to 80°C and acrolein (1.68 mL, 24.4 mmol) is added *via* a syringe pump over a 2 h period. After the addition, the mixture is stirred at 80°C for 1 h and an additional amount of solid ferric chloride is added (4.1 g, 25.3 mmol). The mixture is stirred at 80°C for an extra 24 h and then concentrated under vacuum to give a semi-solid residue. Water (200 mL) is added followed by a 10 N aqueous solution of NaOH (20 mL) and DCM (200 mL). After shaking the mixture for a few min, the solid is filtered over a pad of Celite® and the filtrate is transferred into a separatory funnel. The organic layer is separated and the aqueous layer is extracted with DCM. The combined organic extracts are washed with brine, dried (Na_2SO_4), filtered and concentrated under vacuum to give a brown solid. This solid is triturated in hot CH_3CN and filtered. The solid is discarded and the filtrate is concentrated under vacuum to give a brown semi-solid (2.3 g). This material is purified on a CombiFlash® Companion apparatus on 40 g silica gel column eluted with EtOAc/hexanes gradient. After evaporation of the solvent under vacuum, the desired compound **37c** is isolated as a yellow solid (390 mg, 8% yield).

Step 3:

Compound **37c** is transformed to compound **37d** using the procedure of example **36d**.

Example 38: Synthesis of boronate fragment **38c**



38a **38b** **38c**

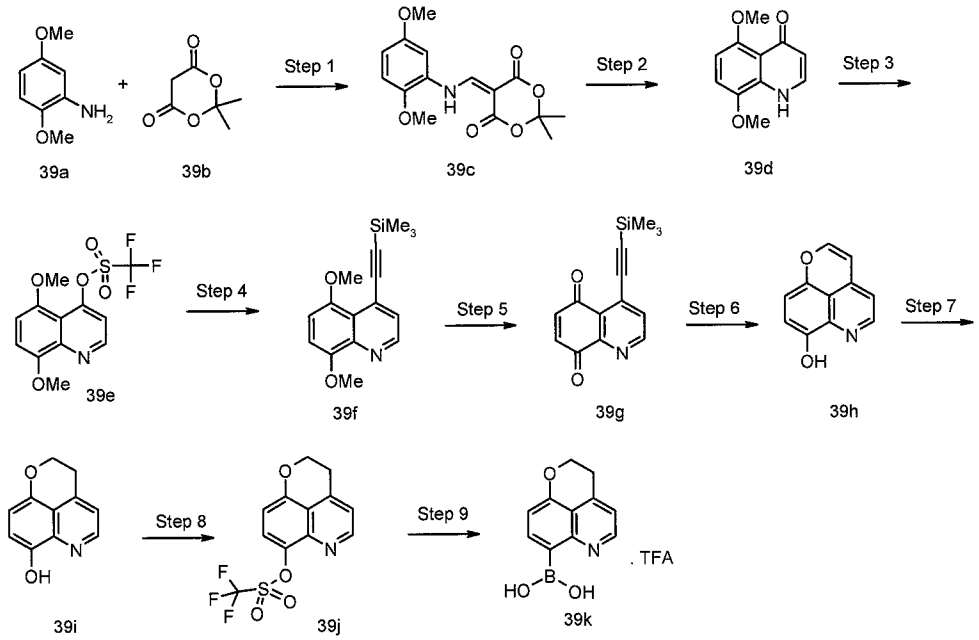
Step 1:

2-bromoaniline **38a** is transformed to compound **39b** using the procedure of example **37c** except that methyl vinyl ketone is used instead of acrolein.

Step 2:

Compound **38b** is transformed to compound **38c** using the procedure of example **36d**.

Example 39: Synthesis of boronate fragment **39k**



39a 39b 39c 39d 39e 39f 39g 39h 39i 39j 39k

Reference: Feliu, L.; Ajana, W.; Alvarez, M.; Joule, J.A. *Tetrahedron* **1997**, *53*, 4511.

Step 1:

Meldrum's acid **39b** (47.04 g, 326 mmol) is dissolved in trimethyl orthoformate (360 mL) and refluxed for 2 h. Then 2,5-dimethoxy aniline **39a** (50 g, 326 mmol) is added and the mixture is refluxed for an extra 5 h. The reaction mixture is cooled down to RT and the solid which formed upon cooling is collected by filtration. It is further crystallized from MeOH to afford compound **39c** as a yellow solid (63 g, 63% yield).

Step 2:

Compound **39c** (62.00 g, 202 mmol) is dissolved in diphenyl ether (310 mL) and refluxed at 240 °C for 30 min. The mixture is then cooled down to RT and n-hexane is added, which causes a brown precipitate to form. This solid is separated by filtration and is washed with n-pentane and n-hexane to remove non-polar impurities and the remaining dark brown solid (compound **39d**) is used as is in the next step (27 g, 65% yield).

Step 3:

A mixture of compound **39d** (30.0 g, 146 mmol), DMAP (3.75 g, 30.7 mmol) and 2,6-lutidine (24.4 mL; 208 mmol) in DCM (1.4 L) is cooled to 0°C and Tf_2O (29.6 mL, 175 mmol) is added slowly at 0°C. The resulting mixture is stirred at 0°C for 2 h and at RT for 1 h. It is then diluted with DCM, washed with H_2O and brine and dried

(Na_2SO_4). The solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (20% EtOAc / petroleum ether). The desired compound **39e** is isolated as a yellow solid (35 g, 70% yield).

Step 4:

A mixture of diisopropylethyl amine (46.5 mL, 267 mmol) in dry DMF (250 mL) is degassed with argon for 30 min and is added to a mixture of compound **39e** (30.0 g, 89.0 mmol), triphenylphosphine (7.70 g, 29.4 mmol), tris(dibenzylideneacetone)di-palladium(0)-chloroform adduct (9.21 g, 8.9 mmol). The resulting mixture is stirred for 5 min at 0°C and TMS acetylene (13.4 g, 136 mmol) is added dropwise. The temperature is raised to RT and the mixture is stirred for 4 h. Diethyl ether and water is added, the aqueous layer is separated and washed with diethyl ether. The combined organic layers are washed with H_2O and brine. After drying on Na_2SO_4, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (30% EtOAc / petroleum ether). Compound **39f** is isolated as a yellow solid (18 g, 70% yield).

Step 5:

A solution of ceric ammonium nitrate (42.3 g, 77.2 mmol) in H_2O (47 mL) is added under argon atmosphere to a solution of compound **39f** (11.0 g, 38.3 mmol) in acetonitrile (366 mL). The reaction mixture is degassed with argon for 10 min and the mixture is stirred at RT for 20 min. Water is then added and the solution is extracted with DCM. The organic extracts are combined, washed with H_2O, brine and dried (Na_2SO_4). The solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (40% EtOAc / petroleum ether). The desired compound **39g** is isolated as a yellow solid (5.0 g, 52% yield).

Step 6:

Compound **39g** (1.80 g, 7.1 mmol) is taken in distilled acetic acid (72 mL) under argon atmosphere. Ammonium chloride (7.55 g, 141 mmol) is added and the reaction is refluxed for 45 min. The reaction mixture is cooled to RT, H_2O is added and the solution is washed with EtOAc. The aqueous layer is neutralized with a saturated aqueous solution of $NaHCO_3$ and is extracted with EtOAc. The combined organic extracts are washed with H_2O, brine and dried (Na_2SO_4). The solvent is removed under reduced pressure to afford compound **39h** as a brown solid (250 mg,

20% yield).

Step 7:

Compound **39h** (230 mg, 1.24 mmol) is dissolved in absolute EtOH (11 mL) and 10% palladium on carbon is added (46 mg) under nitrogen atmosphere. The mixture is stirred for 15 h under one atmosphere of hydrogen. The reaction is degassed with nitrogen, filtered through Celite®, and the Celite® bed is washed with an EtOH-$CHCl_3$ mixture. The solvent is removed under reduced pressure to give compound **39i** as a brown sticky solid (200 mg, 86% yield).

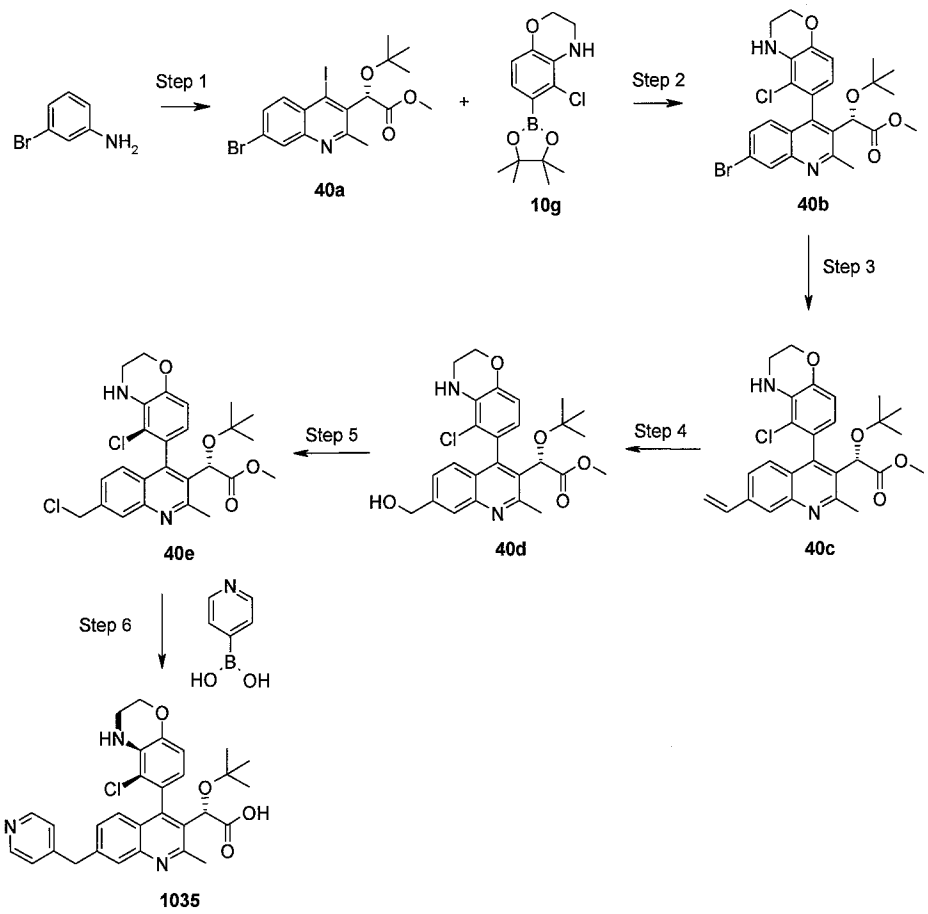
Step 8:

Compound **39i** (600 mg, 3.21 mmol) is taken in dry DCM (30 mL) under nitrogen atmosphere. The solution is cooled to 0°C and triethylamine (0.89 mL, 6.42 mmol) is added dropwise followed by Tf_2O (0.65 mL, 3.87 mmol). The temperature is raised to RT and the reaction mixture is stirred for 2 h. The mixture is diluted with DCM and is washed with H_2O, brine and dried (Na_2SO_4). The solvent is removed under reduced pressure to afford a residue which is purified by flash chromatography (10% EtOAc / hexane). Compound **39j** is isolated as a brown solid (630 mg, 61% yield).

Step 9:

In a dry (oven-dried for 30 min.) 5-mL glass microwave vessel containing a magnetic stirring bar, are added compounds **39j** (250 mg, 0.078 mmol), bis(pinacolato)diborane (250 mg, 0.098 mmol), anhydrous potassium acetate (150 mg, 1.51 mmol), $Pd(PCy_3)_2$ (62.0 mg, 0.091 mmol) and anhydrous, deoxygenated (argon bubbling for 30 min) 1,4-dioxane (4 mL). The vial is capped tightly with a septum-cap and the vessel is flushed with argon. The mixture is stirred at 95°C (oil bath temperature) under an atmosphere of argon for 16 h. The reaction mixture is then concentrated under vacuum, the brown oily residue is dissolved in glacial AcOH (7 mL) and is filtered via 45 µm membrane filter. The dark brown solution is divided into 5x1.5 mL portions and is injected on an automatic preparative reversed-phase HPLC-MS apparatus (CH_3CN/H_2O gradient containing 0.06% TFA, ODS-AQ, C-18 column, 50 x 19 mm, 5-µm particle size). The collected fractions are lyophylized to give the desired compound **39k** as a yellow amorphous solid (115 mg, 45% yield for the TFA salt).

Example 40: Synthesis of compound **1035**



Step 1:

The 7-bromo-4-iodoquinoline **40a** is synthesized from 3-bromoaniline using the same protocols as those described for the preparation of iodoquinoline fragment **1i** in Example 1.

Step 2:

The 7-bromo-4-iodoquinoline **40a** (2.9 g, 5.9 mmol) is combined with boronate **10g** (2 g, 6.8 mmol), potassium carbonate (2.4 g, 17.6 mmol), and $Pd[PPh_3]_4$ (680 mg, 0.59 mmol) in DMF (24 mL). The solution is degassed (Ar) and then heated at 105°C for 5 h. The cooled solution is diluted with EtOAc (200 mL) and washed with brine (3x). The organic phase is dried ($MgSO_4$), filtered and concentrated to dryness. The residue is purified by CombiFlash® Companion to afford compound **40b** as a mixture of atropisomers (670 mg, 21% yield).

Step 3:

To a solution of bromide **40b** (670 mg, 1.26 mmol) in THF (30 mL) is added vinyltributyltin (0.42 mL, 1.38 mmol). Following degassing by bubbling Ar for 10 min under sonication, $PdCl_2[PPh_3]_2$ (0) (88 mg, 0.125 mmol) is added followed by degassing for another 5 min. The reaction mixture is stirred at 75°C for 20 h before being concentrated to dryness. The residue is purified by CombiFlash® Companion to afford compound **40c** (400 mg, 66% yield) which is used as in the following step.

Step 4:

To a solution of compound **40c** (339 mg, 0.7 mmol) in THF (8 mL) and water (4 mL) at RT is added OsO_4 (177 µL, 2.5% soln in t-butanol, 0.014 mmol) followed by NMO (93 mg, 0.8 mmol). The reaction is stirred for 16 h but is not complete. The same quantities of OsO_4 and NMO are again added and stirring continues for an additional 1 h. Sodium periodate (196 mg, 0.92 mmol) is added to generate the intermediate aldehyde. The reaction mixture is poured into a saturated solution of aqueous $Na_2S_2O_3$ and water (50 mL) is added before it is extracted with DCM (3x). The solvent is filtered using a phase separator filter and concentrated. The residue is dissolved in MeOH (10 mL) and treated with $NaBH_4$ (80 mg, 2.1 mmol) at RT for 1 h to give the crude alcohol. A saturated solution of NH_4Cl is added, followed by water (50 mL) and the mixture then is extracted with DCM (3x). The phases are separated using a phase separator filter and the organic phase is concentrated. The residue is purified using the CombiFlash® Companion to afford the alcohol **40d** (171 mg, 50% yield).

Step 5:

To a solution of alcohol **40d** (171 mg, 0.35 mmol) in anhydrous DCM (5 mL) at RT is added anhydrous DMF (1 drop) followed by thionyl chloride (51.5 µL, 0.7 mmol). The resulting solution is stirred for 1 h before being diluted with DCM (5 mL) and then washed with a saturated solution of $NaHCO_3$ (5 mL). After being stirred for 1 min, the mixture is passed through a phase separator filter and concentrated to afford chloride **40e** (160 mg, 90% yield) as a pale yellow solid, which is used as is in the following step.

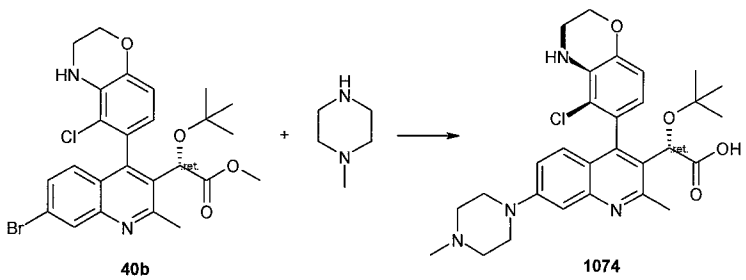
Step 6:

In a vial suitable for microwave, the following are dissolved in anhydrous DMF (2

mL); benzyl chloride **40e** (40 mg, 0.08 mmol), 4-pyridylboronic acid (24 mg, 0.2 mmol), K_3PO_4 (51 mg, 0.24 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol), and triphenylphosphine (8.5 mg, 0.032 mmol). The vial is capped and is degassed by bubbling Ar under sonication for 5 min before being heated at 120°C for 20 min in a microwave. The crude mixture is diluted with EtOAc (200 mL) and washed with brine (3x). The phases are filtered through a phase separator filter and concentrated to dryness. The residue is purified by CombiFlash® Companion to afford the mixture of atropisomeric methyl esters (33 mg, 76% yield) as a pale yellow oil. A solution of this mixture (33 mg) in THF (2 mL) and MeOH (1 mL) and 5N NaOH (72 µL, 0.36 mmol) is stirred at 45°C for 3 h. Acetic acid is added until the solution is acidic and the resulting mixture is then concentrated. Final purification to separate the atropisomers (diastereomers) is performed by preparative HPLC to afford after lyophilization compound **1035** (1.25 mg, 4% yield) as an amorphous solid.

It would be obvious to those skilled in the art that intermediates **40a**, **40b** and **40e** can be used to make a variety of other compounds. Intermediate **40a** can be coupled to any of the boronate fragments described herein in Examples 4-39 via Suzuki coupling reaction to give intermediates analogous to **40b** having different R^4 substituents. Intermediates **40b** and **40e** can then be further modified in a variety of ways that would be evident to those skilled in the art, including directly attached amines and benzylic-type amines derivatives via Buchwald-type coupling or direct alkylation, respectively, with the corresponding amine; the details of the synthesis of two compounds, **1074** (Example 41) and **1071** (Example 42) are described below.

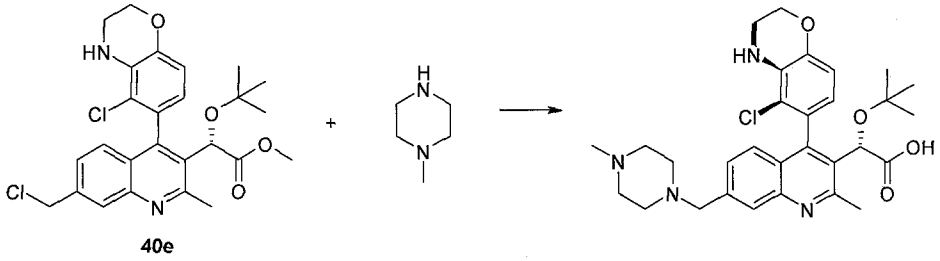
Example 41: Synthesis of compound **1074**



In a vial suitable for microwave reactions is added bromide **40b** (15 mg, 0.028 mmol), acetyltrimethylammonium bromide (2.1 mg, 0.006 mmol), $Pd[(tBu)_3P]_2$ (2.6 mg, 0.003 mmol), 1-methylpiperazine (4 µL, 0.037 mmol), and a solution of 2 M

sodium carbonate (21 µL, 0.042 mmol). The reagents are dissolved in toluene (1.0 mL) before being capped and then submitted directly to the following microwave conditions: 20 min at 145°C. The mixture is concentrated to dryness and purified by CombiFlash® Companion to afford the methyl esters of the atropisomeric mixture (8 mg, 52% yield) as a pale yellow oil. This mixture is dissolved in THF (3 mL) and MeOH (1.5 mL) before being treated with 5N NaOH (17 µL, 0.09 mmol). The solution is heated to 55°C for 16 h before being acidified with AcOH and concentrated to dryness. The mixture is purified by preparative HPLC to separate the atropisomers (diastereomers) and afford after lyophilization, compound **1074** as a yellow amorphous solid (1 mg, 12% yield).

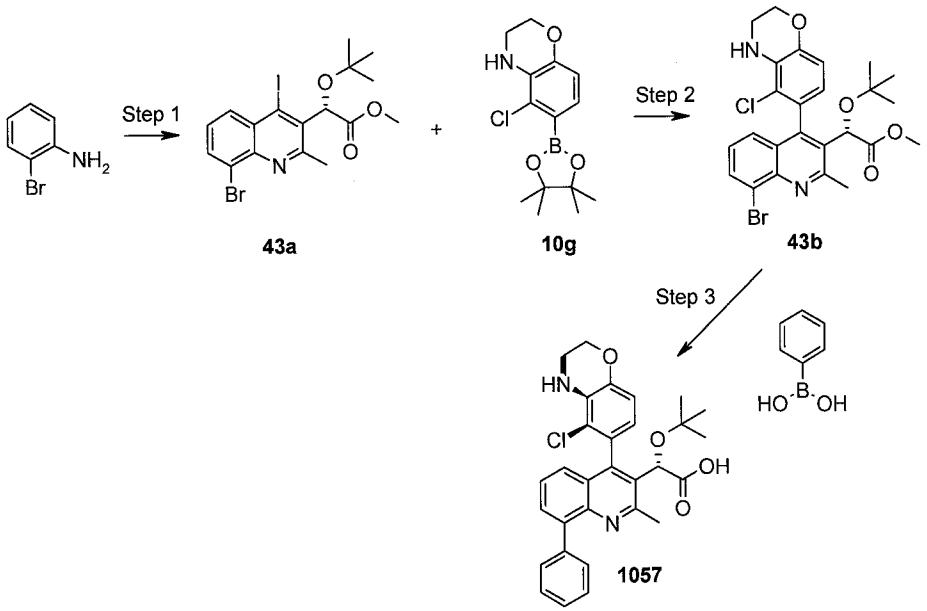
Example 42: Synthesis of compound **1071**



40e 1071

To a solution of chloride **40e** (25 mg, 0.05 mmol) in DMF (3 mL) is added KI (2.5 mg, 0.015 mmol), 1-methylpiperazine (8.8 µL, 0.08 mmol), and triethylamine (17 µL, 0.12 mmol). The reaction mixture is stirred at RT for 24 h. The reaction mixture is diluted with EtOAc (40 mL) and washed with brine (3x). The mixture is filtered through a phase separator filter and concentrated to dryness to afford the atropisomeric mixture of esters (28 mg, 100% yield) as a pale yellow oil. The mixture of esters is dissolved in THF (3 mL) and MeOH (1.5 mL) and 5N NaOH (59 µL, 0.3 mmol) is added. The solution is heated to 55°C for 16 h before being acidified with AcOH and concentrated. The atropisomers (diastereomers) are separated by preparative HPLC to afford (after lyophilization) compound **1071** as orange solid (8.5 mg, 30% yield).

Example 43: Synthesis of compound **1057**



Step 1:

8-bromo-4-iodoquinoline **43a** is synthesized from 2-bromoaniline using the same protocols as those described for the preparation of iodoquinoline fragment **1i** in Example 1.

Step 2:

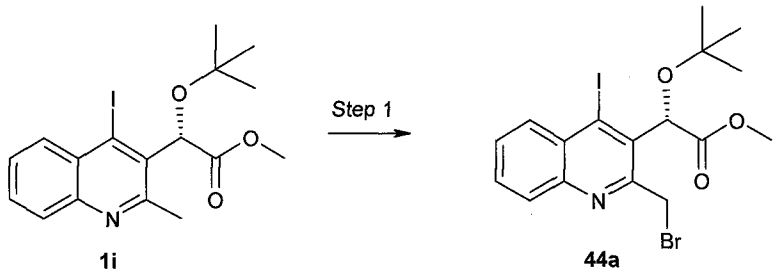
In a suitable microwave vessel, quinoline **43a** (740 mg, 1.5 mmol) is added to boronic ester **10g** (511 mg, 1.73 mmol), $Pd[PPh_3]_4$ (347 mg, 0.3 mmol) and K_2CO_3 (623 mg, 4.5 mmol) in DMF (8 mL). The vessel is sealed and heated for 25 min at 135°C. The cooled reaction mixture is filtered through Celite® and the filtrate is diluted with EtOAc. The organic phase is washed with water, brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product is purified by CombiFlash® Companion to afford a mixture of esters **43b** (426 mg, 53% yield, mixture of two atropisomers).

Step 3:

A mixture of bromide **43b** (60 mg, 0.011 mmol), phenylboronic acid (19.2 mg, 0.016), $Pd[PPh_3]_4$ (26 mg, 0.02 mmol) and K_2CO_3 (47 mg, 0.034 mmol) in DMF (1.5 mL) and water (0.2 mL) is heated to 125°C for 13 min in a microwave. The cooled reaction mixture is filtered through Celite® and the filtrate is diluted with EtOAc. The organic phase is washed with water, brine, dried ($MgSO_4$), filtered and concentrated under

vacuum. The crude product is purified by CombiFlash® Companion to give a crude product mixture (32.8 mg, 55% yield). This mixture is dissolved in THF/MeOH (3 mL/1.5 mL) and treated with 1.0 N NaOH (1 mL, 1.0 mmol). The reaction mixture is stirred at 60°C for 4 h before being acidified to pH 4 with 1.0 N HCl. The mixture is then extracted with DCM, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue is purified by preparative HPLC to afford after lyophilization compound **1057** as an orange solid (9.9 mg, 31% yield).

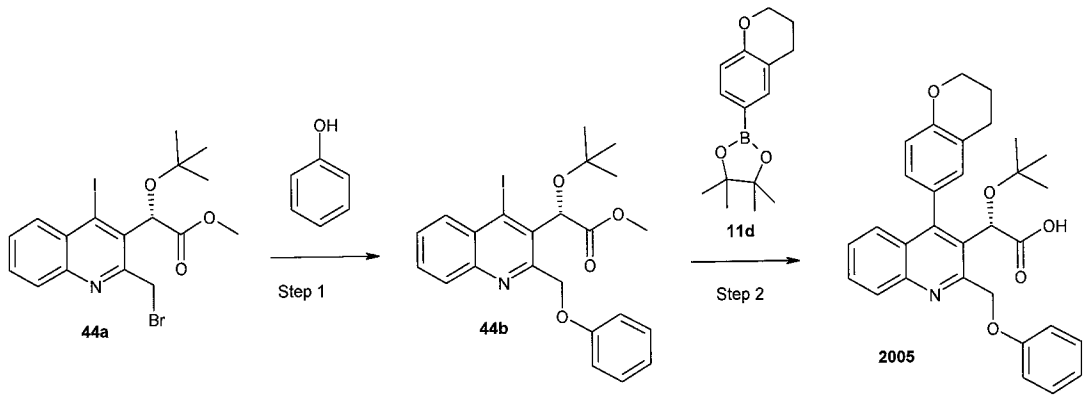
Example 44: Synthesis of C-2 substituted analogs



Step 1:

The 4-iodoquinoline **1i** (3 g, 7.2 mmol) is dissolved in CCl_4 (30 mL) which is subsequently treated with recrystallized NBS (1.4 g, 7.9 mmol) followed by benzoyl peroxide (72 mg, 0.3 mmol). The solution is heated to 75°C for 24 h. The solvent is removed and the crude product taken up in EtOAc (250 mL), washed with brine, before being dried (Na_2SO_4), filtered and concentrated to afford the crude product as an amber gum. This material is purified by CombiFlash® Companion to afford bromide **44a** (2.5 g, 70% yield).

It is clear for a person skilled in the art that various analogs can be prepared from compound **44a** using a variety of appropriate metal alkoxides (in the case of alcohols) or appropriate anions for nitrogen based nucleophiles; as an example, the synthesis of compound **2005** is shown below



Step 1:

Phenol (19 mg, 0.20 mmol) is dissolved in DMF (1.0 mL) before being treated with K_2CO_3 (15 mg, 0.10 mmol). The potassium salt is allowed to pre-form over a period of 1 h before a solution of bromide **44a** is added (50 mg, 0.10 mmol). The aryl ether is allowed to form overnight at RT. The mixture is taken up in EtOAc (15 mL) and washed with brine before being dried (Na_2SO_4), filtered and concentrated. The crude product is purified by CombiFlash® Companion to give the aryl ether **44b** as a colorless gum (36 mg, 70% yield).

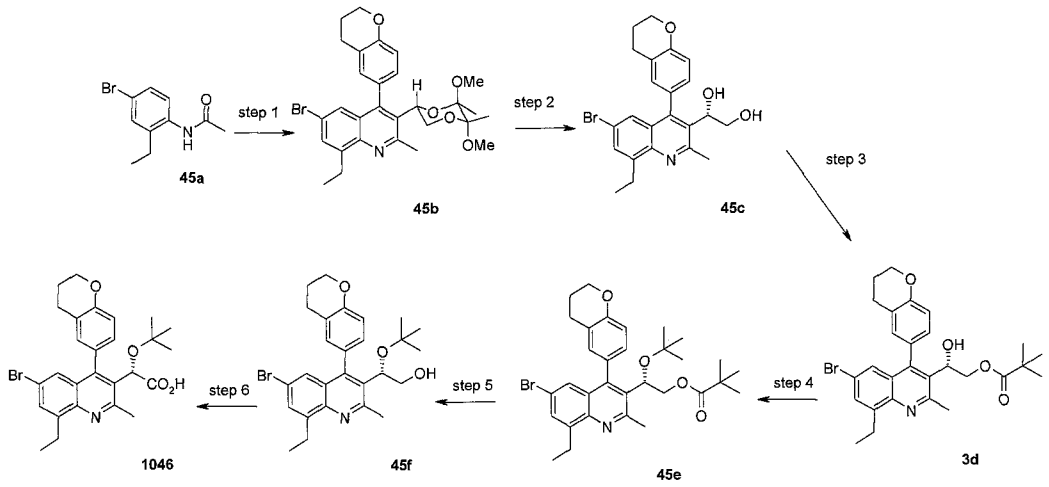
Step 2:

In a microwave vessel is added ether **44b** (36 mg, 0.07 mmol), the boronic ester **11d** (24 mg, 0.09 mmol), K_2CO_3 (29 mg, 0.21 mmol) and the catalyst $Pd(PPh_3)_4$ (8.3 mg, 0.01 mmol) all dissolved in DMF/H_2O(1 mL/0.1 mL). The vessel is capped and submitted to microwave conditions at 110°C for 15 min. The reaction mixture is diluted with EtOAc and subsequently washed with water. The organic phase is further washed with brine, dried ($MgSO_4$), filtered and concentrated. The material is purified by CombiFlash® Companion to afford the methyl ester of the desired product (23 mg, 63% yield) as a white solid. This material is dissolved in THF (1 mL) and MeOH (0.6 mL) and NaOH (1 N, 0.33 mL, 0.33 mmol) is added. The mixture is stirred at 50°C for 16 h. The mixture is concentrated *in vacuo* before being purified by reversed phase preparative HPLC to afford after lyophilization compound **2005** as a yellow amorphous solid (13.5 mg, 60% yield).

It would be obvious to those skilled in the art that intermediate **44a** can be used with other nucleophiles to displace the primary bromide (as in the preparation of **44b** from

44a), followed by Suzuki coupling with any boronate fragment described in this application to produce a variety of other compounds (for example, the production of compound 2005 from **44b**).

Example 45: Synthesis of compound **1046**



Step 1:

Triflic anhydride (190 µL, 1.13 mmol) is added via syringe over 1 min to a stirred mixture of amide **45a** (250 mg, 1.0 mmol) and 2-chloropyridine (130 µL, 1.4 mmol) in DCM (2 mL) at -78°C. After 5 min, the reaction flask is placed in an ice-water bath and warmed to 0°C. Alkyne **2c** (232 mg, 0.70 mmol) in DCM (1mL) is added *via* syringe. The resulting solution is allowed to warm to RT. After stirring for 30 min, Et_3N (1 mL) is added and the mixture partitioned between DCM (50 mL) and brine (50 mL). The organic layer is washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue is then purified by CombiFlash® Companion giving quinoline **45b** (380 mg, 97% yield).

Step 2:

Quinoline **45b** (380 mg, 0.68 mmol) is dissolved in TFA/water (10:1, 10.5 mL) and the reaction is stirred at RT. After 30 min, the reaction mixture is concentrated under reduced pressure, diluted with saturated $NaHCO_3$ (5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give diol **45c** (299 mg, >99% yield).

Step 3:

Trimethylacetyl chloride (100 µL, 0.81 mmol) is added to a 0°C solution of diol **45c** (299 mg, 0.68 mmol) and Et_3N (280 µL, 2.0 mmol) in DCM (3.8 mL). The reaction is allowed to come to RT and stir overnight. The reaction is quenched with water (10 mL) and washed with EtOAc (10 mL). The organic layer is dried over Na_2SO_4 and concentrated. The mixture is purified by CombiFlash® Companion to give ester **45d** (85 mg, 24% yield).

Step 4:

One drop of 70% perchloric acid is added to a stirred solution of alcohol **45d** (85 mg, 0.161 mmol) dissolved in *tert*-butyl acetate (1.8 mL) at RT and the mixture stirred overnight. The reaction is quenched by addition of saturated $NaHCO_3$ (5 mL) and the mixture extracted with EtOAc (5 mL). The organic layer is dried over Na_2SO_4, filtered and the solvent evaporated. The residue is purified by CombiFlash® Companion to give *tert*-butyl ether **45e** (40 mg, 43% yield).

Step 5:

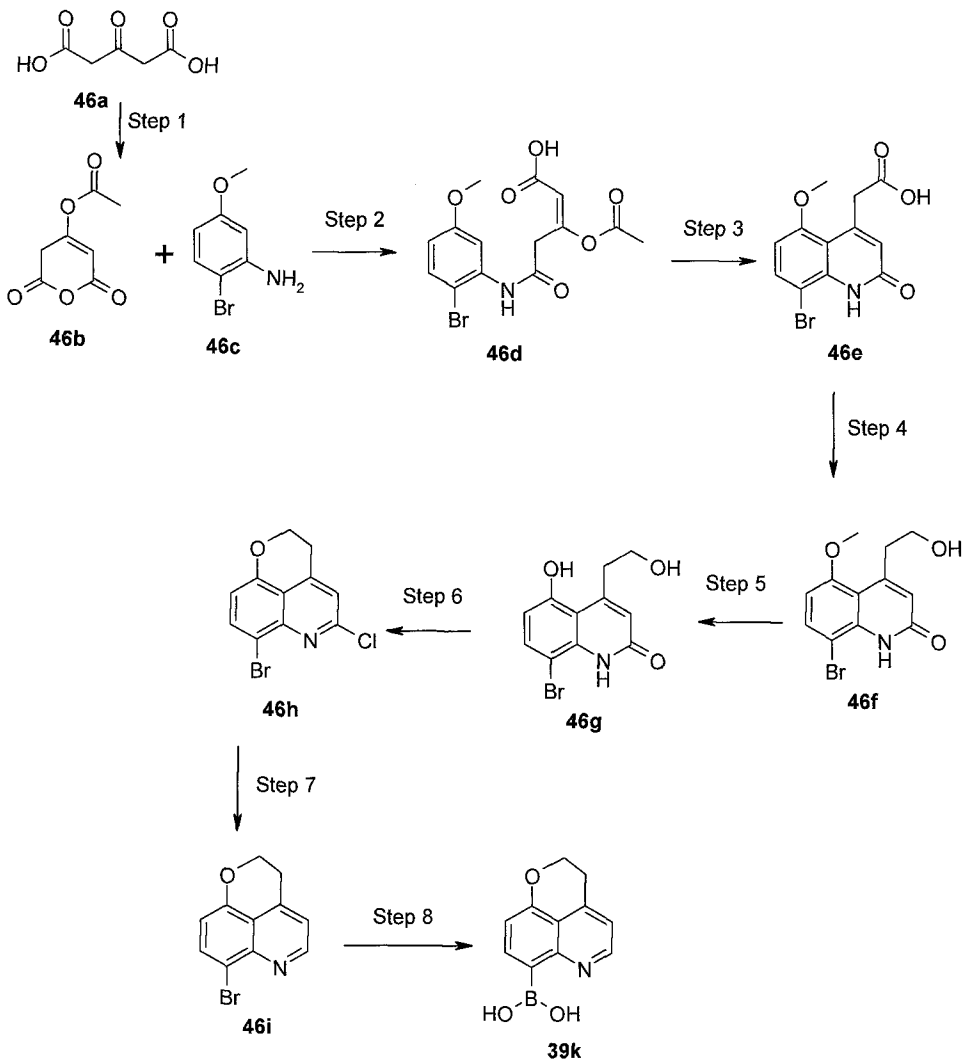
$LiBH_4$ in THF (2 M, 69 µL, 0.14 mmol) is added to a solution of ester **45e** (40 mg, 0.069 mmol) dissolved in THF (1 mL) and the reaction mixture is stirred overnight at RT. Excess reagent is quenched with HCl (three drops, lots of effervescence) and the mixture neutralized with $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give crude alcohol **45f** (27 mg, 79% yield), which was used directly in the next step.

Step 6:

Dess-Martin periodinane (30 mg, 0.07 mmol) is added to a solution of alcohol **45f** (27 mg, 0.54 mmol) dissolved in DCM (0.4 mL). After 2 h, the reaction mixture is then applied to a plug of SiO_2 (1.5 x 1 cm) and the product eluted with 1:1 hexanes/ EtOAc (20 mL). The filtrate is evaporated to give the crude aldehyde which is then dissolved in 1:1 THF/tBuOH (2 mL) and 2,3-dimethyl-2-butene (1M in THF, 0.5 mL, 0.5 mmol) is added. A separate solution of $NaClO_2$ (39 mg, 0.44 mmol) and NaH_2PO_4 (32 mg, 0.27 mmol) in water (1 mL) is added to the first solution and the reaction stirred at RT. After 20 min, the reaction is diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layer is dried over Na_2SO_4 and

concentrated. The residue is purified by preparative HPLC to give carboxylic acid **1046** (6 mg, 20% yield).

Example 46: Alternative Synthesis of boronate fragment **39K**



Step 1:

1,3-acetonedicarboxylic acid **46a** (30 g, 205.3 mmol) is added in portions to acetic anhydride (55 g, 587.7 mmol) and the mixture is stirred at 35°C for 23 h. The mixture is filtered and the filtrate is diluted with benzene (200 mL) and the solution stored at 5°C for 3 h. The suspension formed is filtered and the solid is dried under vacuum to give compound **46b** as a pale yellow solid (26.9 g, 70% yield).

Step 2:

To a stirred solution of aniline **46c** (7.5 g, 44 mmol) in AcOH (50 mL) is added **46b** (8.0 g, 40 mmol) portionwise. Following addition, the reaction mixture is warmed to 35°C. After 2 h, the reaction mixture is cooled to RT and poured in ice/water (600 mL). The resulting precipitate is isolated by filtration, rinsed with water (100 mL) and dried under vacuum to give **46d** (9.1 g, 61% yield).

Step 3:

Compound **46d** (5.7 g, 15.4 mmol) is added portionwise to concentrated sulfuric acid (20 mL) at RT, temperature of the reaction mixture is kept below 30°C during addition. The mixture is stirred at RT for 30 min and then poured in ice/water (400 mL). The resulting precipitate is isolated by filtration, rinsed with water and dried under vacuum to give **46e** (3.5 g, 72% yield) as a white solid.

Step 4:

The borane solution (1.0 M in THF, 10.5 ml, 10.5 mmol) is added dropwise to an ice cold solution of quinolone **46e** (1.5 g, 4.8 mmol) in dry THF (40 mL) under a N_2 atmosphere. After the addition, the reaction is allowed to warm to RT and stirred for 22 h (reaction not completed by HPLC, 15% starting material). An extra equivalent of BH_3 is added at 0°C and the reaction mixture is heated to 45°C for 2 h. The reaction mixture is carefully quenched witn 1.0 N NaOH (10 mL) and THF is removed under vacuum. The mixture is poured in EtOAc (100 mL) and the desired compound crashed out of the solution under these conditions. The solid recovered by filtration is dried under vacuum to give compound **46f** as a grey solid (1.1 g, 79% yield).

Step 5:

To a solution of **46f** (1.1 g, 3.8 mmol) in DCM (60 mL) at -78°C is added dropwise a 1.0 M BBr_3 solution (23 mL, 23 mmol). The cooling bath is removed after 1 h and the mixture is stirred at RT for 16 h (by HPLC, ~30% cyclized product **46h** is formed). The mixture is poured in ice/water (100 mL) and the white precipitate that formed is filtered and dried under vacuum to give **46g** (773 mg , 71% yield).

Step 6:

To a solution of compound **46g** (773 mg, 2.27 mmol) in THF (30 mL) is added PPh_3

(928 mg, 3.5 mmol) followed by DIAD (0.69 ml, 3.5 mmol) (dropwise) and the solution is stirred at RT for 2 h. The reaction mixture is concentrated under vacuum and the crude product is directly added portionwise to $POCl_3$ (2 mL) at RT. The reaction mixture is stirred at 100°C for 45 min and then cooled to room temperature. The mixture is concentrated under vacuum (to remove $POCl_3$) and the crude product is diluted with DCM. The organic phase is washed with 1.0 N NaOH, water, and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product is purified by CombiFlash® Companion (Hexanes/EtOAc 9/1 to 1/1) to give **46h** as a pale yellow solid (445 mg, 91% yield).

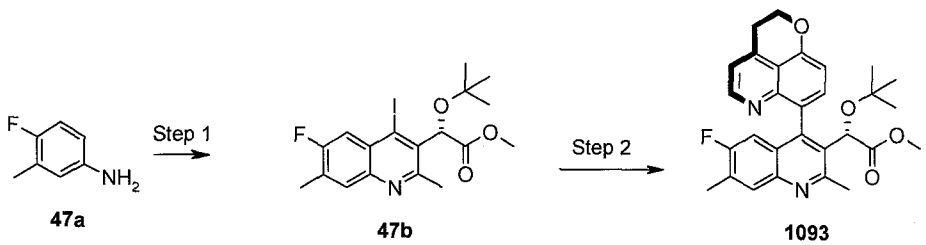
Step 7:

To a solution of chloroquinoline **46h** (30 mg, 0.1 mmol) in TFA (1 mL) is added zinc (34 mg; 0.5 mmol). The reaction mixture is stirred at RT for 16 h. The mixture is filtered, concentrated under vacuum, then diluted with 1.0 N NaOH (5 mL) and extracted with DCM (3x). The combined organic extracts are washed with water and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by combi flash (Hexanes/EtOAc 6/4 to 4/6) to give **46i** as a pale yellow solid (26 mg, quantitative yield).

Step 8:

The reaction is done following a similar procedure as described in step 9 of example 39 except starting with **46i** and using $Pd(Ph_3)_4$ as catalyst to give **39k** as a white solid.

Example 47: Synthesis of compound **1093**



47a **47b** **1093**

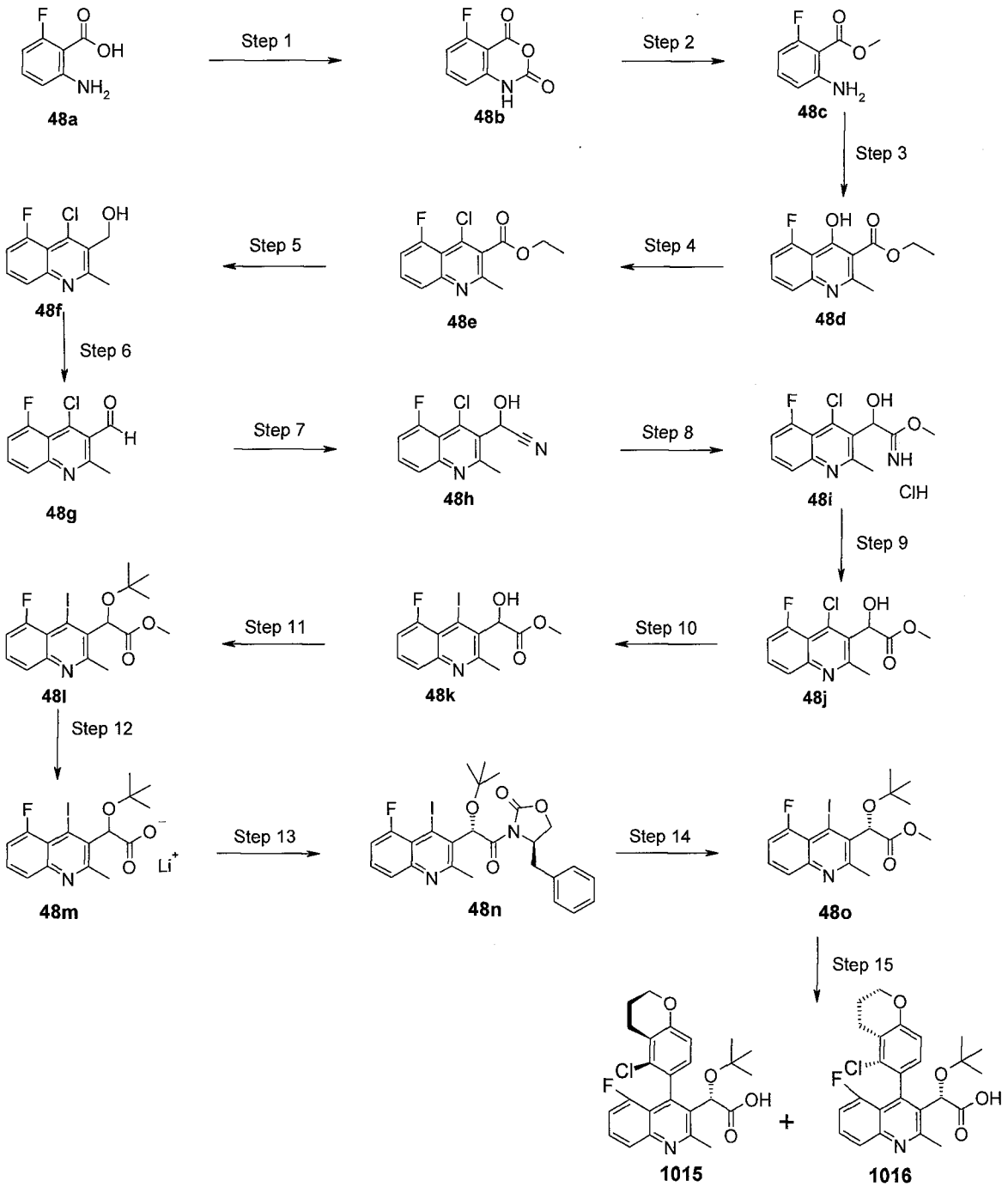
Step 1:

Iodoquinoline **47a** is synthesized from aniline **46a** using the same protocols as those described for the preparation of iodoquinoline fragment **1i** in Example 1.

Step 2:

Reaction is carried out exactly as described in step 2 of example 43 using iodo **47b** and boronic acid **39k** to give compound **1093**.

Example 48: Synthesis of compound **1015** and **1016**



Step 1:

A 1.93 M phosgene solution in toluene (106.9 mL, 206.3 mmol) is added to a vigorously stirred suspension of anthranilate **48a** (25.6 g, 165 mmol) in toluene (150 mL) in a pressure bottle. The reaction vessel is sealed and heated to 100°C behind safety shield overnight. An additional amount of phosgene solution (42.7 mL; 82.5 mmol) is added to the cooled mixture and the reaction mixture is heated to 100°C for an additional 4 h then is allowed to cool slowly to 0°C. The resulting suspension is filtered, the solid is washed with cold toluene and air dried overnight to give **48b** (28.1 g, 94% yield) as a white solid.

Step 2:

A solution of **48b** (28.1 g, 155 mmol) and DMAP (1.89 g, 15.5 mmol) in MeOH (500 mL) is heated at reflux for 24 h. The cooled reaction mixture is concentrated under reduced pressure and diluted with EtOAc (200 mL). The resulting solution is washed twice with phosphate buffer pH 6.0, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give compound **48c** (26.1 g, 99% yield).

Step 3:

A solution of **48c** (26.0 g, 154 mmol), ethyl 3-ethoxybut-2-enoate (25.5 g, 161 mmol) and *p*-TsOH monohydrate (75.3 mg, 0.40 mmol) in o-xylene (500 mL) is heated (bath temp: 158°C) for 15 h using a Dean-Stark trap to remove the produced EtOH. The mixture is cooled to RT and added slowly (25 min) to an ice-cold solution of 21% (w/w) NaOEt (60.26 mL, 161.5 mmol) in EtOH. The resulting brownish solution is heated to 80°C for 4 h. The resulting suspension is allowed to cool to RT and is concentrated under reduced pressure. Water (400 mL) is added to the residual solid and the mixture is washed with Et_2O (2 x 400 mL). The aqueous phase is cooled to 0°C and slowly acidified to pH 4 using 1 N HCl. The resulting suspension is filtered and the recovered solid is washed with dilute HCl (pH 4, 25 mL), dried under reduced pressure to give compound **48d** (24.1 g, 63% yield) as a pale yellowish solid.

Step 4:

A mixture of **48d** (24.1 g, 96.7 mmol) and $POCl_3$ (250 mL) is heated at reflux for 1 h. The cooled reaction mixture is concentrated under reduced pressure. The residue is poured into ice-water (500 mL) and stirred vigorously. The pH is adjusted to 6.5

using aqueous 5 N NaOH. The mixture is extracted with EtOAc and the combined organic layers are washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give compound **48e** (25.2 g, 97% yield) as a black tar. The crude product is used as in next step.

Step 5:

A solution of 1 M DIBAL-H in toluene (200 mL, 200 mmol) is added (45 min) to a cold (-78°C) solution of **48e** (25.2 g, 94.1 mmol) in DCM (300 mL). The reaction mixture is stirred at RT for 30 min then re-cooled to -78°C. An aqueous 20% Rochelle salt solution (200 mL) is added and the mixture is allowed to warm to RT. The resulting suspension is diluted with DCM (300 mL) and the layers are separated. The aqueous layer is extracted twice with DCM. The combined organic layers are dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting solid is dried at 50°C under reduced pressure to give alcohol **48f** (15.18 g, 71% yield) as a brown solid.

Step 6:

Et_3N (18.5 mL, 133 mmol) is added to a cool solution of **48f** (10.0 g, 44.3 mmol) in DMSO (50 mL). Pyridine·SO_3 complex (17.6 g, 111 mmol) is next added to the mixture in small portions over 5 min. The reaction mixture is stirred for 1 h then is poured in ice cold water (400 mL) and the resulting suspension is filtered. The solid is dissolved in DCM (200 ml) and the solution is dried ($MgSO_4$), filtered and concentrated under reduced pressure to give aldehyde **48g** (9.01 g, 91% yield) as a brown solid.

Step 7:

ZnI_2 (6.42 g, 20.1 mmol) and TMSCN (10.7 mL, 80.5 mmol) are successively added to an ice-cold solution of aldehyde **48g** (9.00 g, 40.2 mmol) in DCM (300 mL). The mixture is stirred at 0°C for 1 h and at RT for 4 h. The reaction mixture is washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give cyanohydrin **48h** (12.0 g, 93% yield) as a tan crystalline solid.

Step 8:

A saturated solution of hydrogen chloride in MeOH (80 mL) is added to a suspension of **48h** (12.2 g, 37.8 mmol) in MeOH (20 mL). The reaction mixture is stirred at RT

for 2 h. N_2 is bubbled in the mixture for 30 min to remove excess HCl. The mixture is concentrated under reduced pressure to give compound **48i** (11.1 g, 92% yield) as a tan crystalline solid.

Step 9:

A solution of **48i** (11.05 g, 34.6 mmol) in aqueous 1 N HCl (150 mL) is stirred for 1 h at RT. The reaction mixture is diluted with water (100 mL) and filtered over celite®. The pH of the aqueous filtrate is adjusted to 7.5 using aqueous 5 N NaOH. The solution is extracted twice with EtOAc. The combined organic layers are washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give methyl ester **48j** (10.2 g, 104% yield) as a tan solid.

Step 10:

Chloroquinoline **48j** (10.2 g, 36.0 mmol) is dissolved in a solution of 4 N HCl in 1,4-dioxan (100 mL). The solution was concentrated under reduced pressure. A mixture of the resulting HCl salt and NaI (27.0 g, 180 mmol) in MeCN (250 mL) is heated at reflux for 1h. The cooled reaction mixture is diluted with EtOAc (300 mL) and the mixture is washed with aqueous 5% $NaHCO_3$ solution and aqueous 10% $Na_2S_2O_4$ solution. The organic layer is dried ($MgSO_4$), filtered and concentrated under reduced pressure to give iodoquinoline **48k** (11.3 g, 84% yield) as a tan solid.

Step 11:

$HClO_4$ (1.17 mL, 13.6 mmol) is added to a suspension of **48k** (3.40 g, 9.06 mmol) in *t*-butyl acetate (100 mL) and DCM (150 mL). The reaction mixture is stirred at RT overnight then is diluted with EtOAc (150 mL). The solution is washed twice with aqueous 5% $NaHCO_3$ solution, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (Combi-Flash; EtOAc / hexane) to give t-butylether **48l** (2.76 g, 71% yield) as a white solid.

Step 12:

A mixture of ester **48l** (5.01 g, 11.6 mmol) and LiOH hydrate (487 mg, 11.6 mmol) in THF (30 mL), MeOH (15 mL) and water (15 mL) is heated at reflux for 11 h. The reaction mixture is concentrated under reduced pressure. The residue is successively taken in EtOH (2 × 150 mL) and toluene (100 mL) and concentrated under reduced pressure to remove traces of water. The solid is dried under reduced

pressure to give lithium salt **48m** (5.10 g, 104% yield) as a pale yellow solid.

Step 13:

Pivaloyl chloride (1.43 mL, 11.6 mmol) is added to an ice-cold solution of **48m** (5.08 g, 11.6 mmol) in THF (100 mL). The mixture is stirred at 0°C for 30 min then cooled to -78°C (mixed anhydride solution). A solution of 2.5 M *n*-BuLi in hexane (4.87 mL, 12.2 mmol) is added dropwise (until an orange color persisted) to a cold solution (-40°C) of (R)-(+)-4-benzyl-2-oxazolidinone (2.16 g, 12.2 mmol) and triphenylmethane (10 mg) in THF (30 mL). The resulting mixture is cooled to -78°C and rapidly cannulated into the mixed anhydride solution prepared previously. The reaction mixture is stirred at -78°C for 30 min then is allowed to warm to RT and stirred at this temperature for 30 min. Aqueous 5% $KHCO_3$ solution (4 mL) is added and the mixture is concentrated under reduced pressure. The residue is diluted with EtOAc (250 mL) and the solution is successively washed with aqueous 5% $KHCO_3$ solution and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (Combi-Flash; EtOAc/hexanes) to give the desired diasteroisomer **48n** (1.34 g, 20% yield; higher retention time on reverse phase HPLC).

Step 14:

DBU (416 µL, 2.78 mmol) and NaI (1.74 g, 11.6 mmol) are successively added to a cold (-5°C) solution of oxazolidinone **48n** (1.34 g, 2.32 mmol) in THF (6 mL) and MeOH (12 mL). After 1 h the reaction mixture is concentrated under reduced pressure and EtOAc (100 mL) is added. The solution is washed with aqueous phosphate buffer pH 6.0 and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (Combi-Flash; EtOAc/hexanes) to give methyl ester **48o** (718 mg, 72% yield) as a yellowish crystalline solid.

Step 15:

Reaction is carried out exactly as described in step 2 of example **43** using iodo **48o** and boronic acid **6i** to give compound **1015** and **1016**.

Example 49: C8166 HIV-1 Luciferase Assay (EC_{50})

C8166 cells are derived from a human T-lymphotrophic virus type 1 immortalized but

nonexpressing line of cord blood lymphocytes (obtained from J. Sullivan) and are highly permissive to HIV-1 infection. The pGL3 Basic LTR/TAR plasmid is made by introducing the HIV-1 HxB2 LTR sequence from nucleotide -138 to +80 (Sca1-HindIII) upstream of the luciferase gene in the pGL3 Basic Vector (a promoterless luciferase expression vector from Promega catalogue #E1751) with the gene for blasticidine resistance cloned in. The reporter cells are made by electroporating C8166 cells with pGL3 Basic LTR/TAR and selecting positive clones with blasticidine. Clone C8166-LTRluc #A8-F5-G7 was selected by 3 consecutive rounds of limiting dilution under blasticidine selection. Cultures are maintained in complete media (consisting of: Roswell Park Memorial Institute medium (RPMI) 1640 + 10% FBS + 10^{-5} M β-mercaptoethanol + 10 μg/mL gentamycin) with 5 μg/mL blasticidine, however, blasticidine selection is removed from the cells before performing the viral replication assay.

Luciferase Assay Protocol

Preparation of Compounds

Serial dilutions of HIV-1 inhibitor compounds are prepared in complete media from 10 mM DMSO stock solutions. Eleven serial dilutions of 2.5X are made at 8X desired final concentration in a 1 mL deep well titer plate (96 wells). The 12th well contains complete media with no inhibitor and serves as the positive control. All samples contain the same concentration of DMSO (≤ 0.1% DMSO). A 25 μL aliquot of inhibitor is added, to triplicate wells, of a 96 well tissue culture treated clear view black microtiter plate (Corning Costar catalogue # 3904). The total volume per well is 200 μL of media containing cells and inhibitor. The last row is reserved for uninfected C8166 LTRluc cells to serve as the background blank control and the first row is media alone.

Infection of Cells

C8166 LTRluc cells are counted and placed in a minimal volume of complete RPMI 1640 in a tissue culture flask (ex. 30 X 10^6 cells in 10 mL media/25 cm^2 flask). Cells are infected with HIV-1 or virus with variant integrase generated as described below at a molecules of infection (moi) of 0.005. Cells are incubated for 1.5 h at 37 °C on a rotating rack in a 5% CO_2 incubator and re-suspended in complete RPMI to give a final concentration of 25,000-cells/175 μL. 175 μL of cell mix is added to wells of a 96 well microtiter plate containing 25 μL 8X inhibitors. 25,000 uninfected C8166-

LTRluc cells/well in 200 μL complete RPMI are added to the last row for background control. Cells are incubated at 37 °C in 5% CO_2 incubator for 3 days.

Luciferase Assay

50 μL Steady Glo (luciferase substrate $T_{1/2}$=5 hours Promega catalogue # E2520) is added to each well of the 96 well plate. The relative light units (RLU) of luciferase is determined using the LUMIstar Galaxy luminometer (BMG LabTechnologies). Plates are read from the bottom for 2 seconds per well with a gain of 240.

The level of inhibition (% inhibition) of each well containing inhibitor is calculated as follows:

$$\%\cdot inhibition = \left(1 - \left[\frac{RLU\cdot well - RLU\cdot blank}{RLU\cdot control - RLU\cdot blank}\right]\right) * 100$$

The calculated % inhibition values are used to determine EC_{50}, slope factor (n) and maximum inhibition (I_{max}) by the non-linear regression routine NLIN procedure of SAS using the following equation:

$$\%\cdot inhibition = \frac{I_{max} \times [inhibitor]^n}{[inhibitor]^n + IC_{50}{}^n}$$

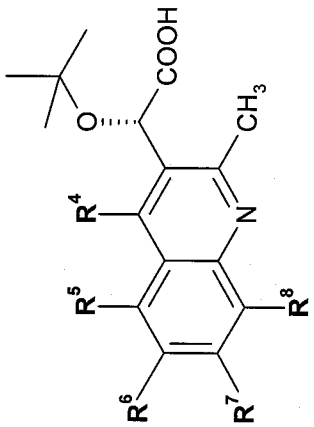
TABLES OF COMPOUNDS

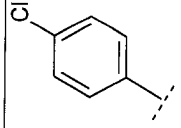
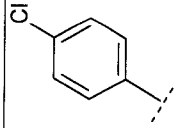
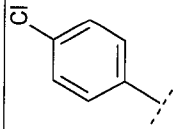
Compounds of the invention shown in Tables 1 to 4 are integrase inhibitors. Representative compounds selected from Tables 1 to 3 below have EC_{50} values of no more than 20 μM when tested in the HIV-1 luciferase assay of Example 46.

Retention times (t_R) for each compound are measured using the standard analytical HPLC conditions described in the Examples. As is well known to one skilled in the art, retention time values are sensitive to the specific measurement conditions. Therefore, even if identical conditions of solvent, flow rate, linear gradient, and the like are used, the retention time values may vary when measured, for example, on different HPLC instruments. Even when measured on the same instrument, the values may vary when measured, for example, using different individual HPLC columns, or, when measured on the same instrument and the same individual

column, the values may vary, for example, between individual measurements taken on different occasions.

TABLE 1

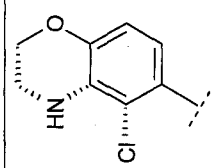
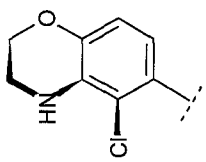
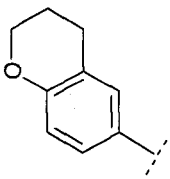
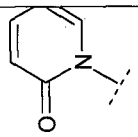
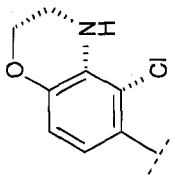
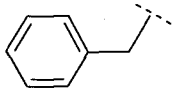
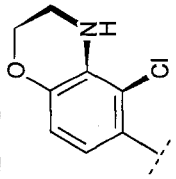
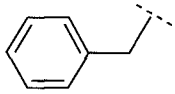


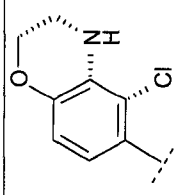
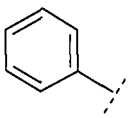
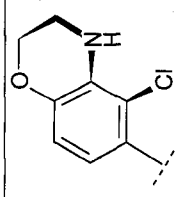
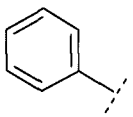
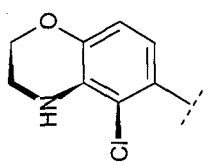
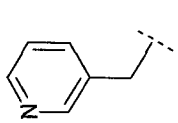
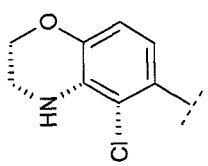
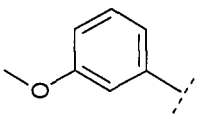
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1001		F	H	H	H	4.7	402.1 / 404.1
1002		H	$-OCH_3$	H	H	4.6	414.1 / 416.1
1003		H	H	$-OCH_3$	H	4.7	414.2 / 416.1

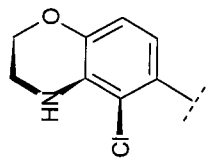
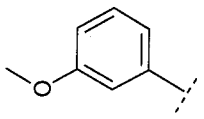
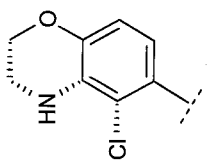
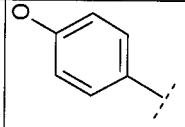
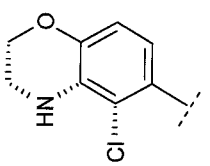
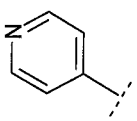
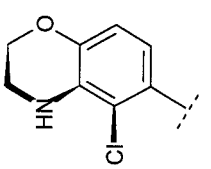
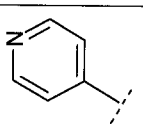
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1004		H	H	H	F	5.1	402.1 / 404.1
1005		F	H	H	H	5.7	420.1 / 422.1
1006		H	-CH=CH$_2$	H	H	5.4	410.1 / 412.1
1007		F	H	H	H	4.9	442.2
1008		F	H	H	H	5.1	442.1

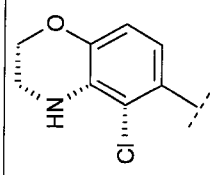
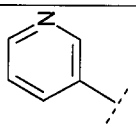
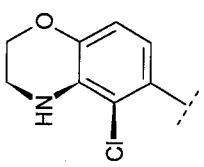
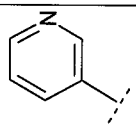
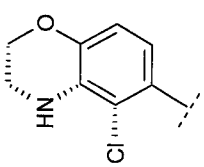
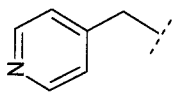
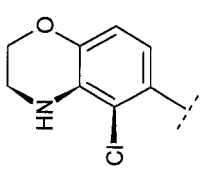
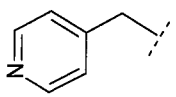
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1009		F	H	H	H	4.9	442.1
1010		F	H	H	H	5.2	442.1
1011		H	-CN	H	H	5.4	409.2 / 411.2
1012		H	-C(=O)H	H	H	4.9	412.2 / 414.2
1013		H	$-CH_2OH$	H	H	4.2	414.2 / 416.2

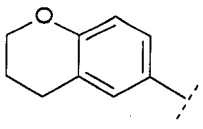
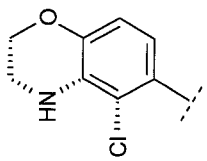
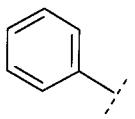
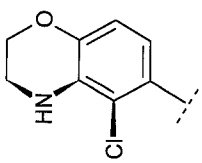
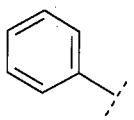
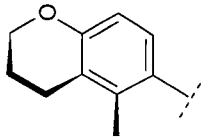
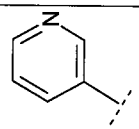
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1014		H	-C≡CH	H	H	5.2	408.2 / 410.2
1015		F	H	H	H	5.0	458.1 / 460.1
1016		F	H	H	H	5.2	458.1 / 460.1
1017		F	H	H	H	4.9	438.2
1018		H	H	H	Br	8.8	462.1 / 464.1 / 466.1

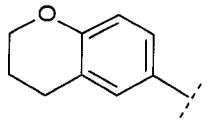
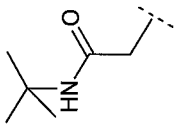
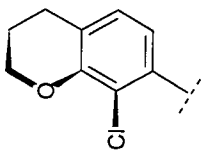
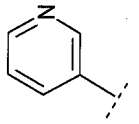
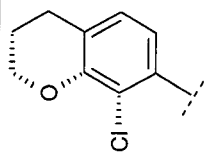
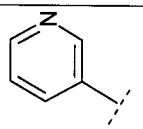
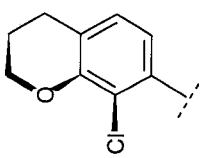
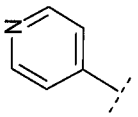
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1019		F	H	H	H	3.9	459.2 / 461.2
1020		F	H	H	H	4.2	459.2 / 461.2
1021		H	H		H	4.5	499.3
1022		H	H		H	5.4	531.2 / 533.2
1023		H	H		H	5.4	531.2 / 533.2

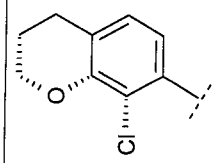
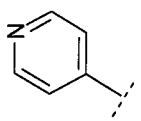
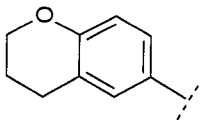
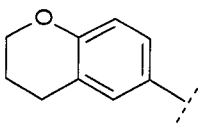
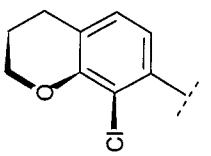
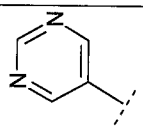
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1024		H	H		H	5.4	517.3 / 519.3
1025		H	H		H	5.6	517.3 / 519.3
1026		H	H		H	3.7	532.3 / 534.2
1027		H	H		H	5.5	547.3 / 549.3

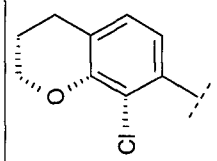
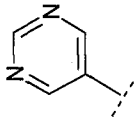
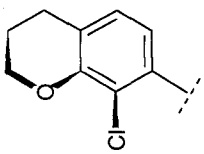
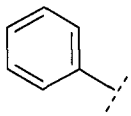
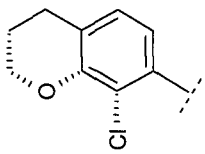
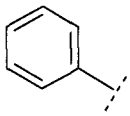
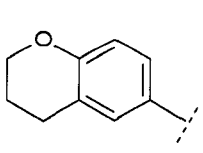
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1028		H	H		H	5.7	547.3 / 549.3
1029		H	H		H	5.4	547.3 / 549.3
1030		H	H		H	3.7	518.3 / 520.3
1031		H	H		H	3.8	518.3 / 520.3

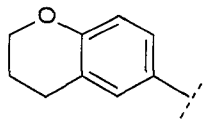
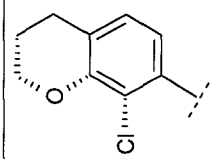
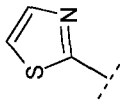
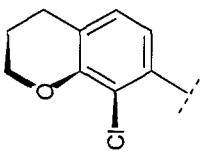
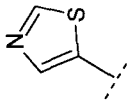
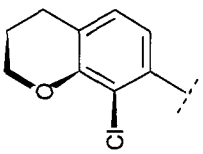
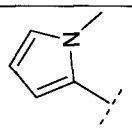
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1032		H	H		H	3.7	518.3 / 520.3
1033		H	H		H	3.8	518.3 / 520.3
1034		H	H		H	3.4	532.3 / 534.3
1035		H	H		H	3.6	532.3 / 534.3

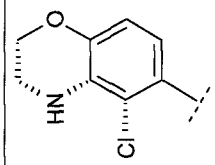
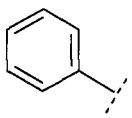
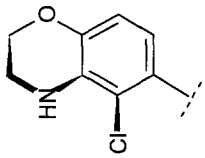
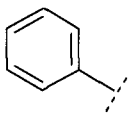
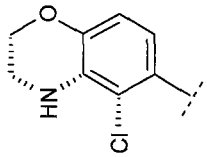
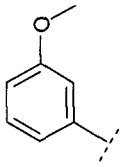
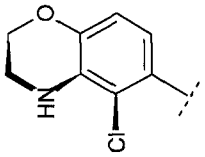
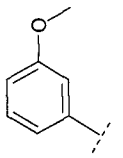
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1036		H	Br	H	$-CH_3$	5.4	498.2 / 500.2
1037		H		H	H	5.3	517.2 / 519.2
1038		H		H	H	5.5	517.2 / 519.2
1039		H	H		H	4.2	497.3

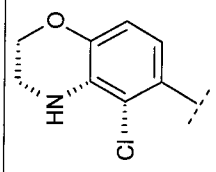
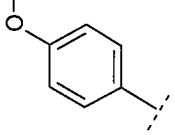
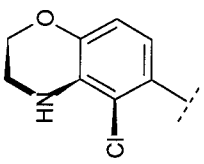
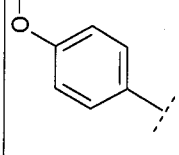
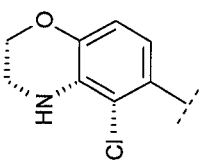
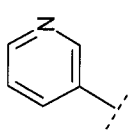
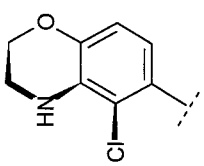
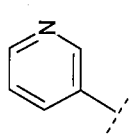
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1040		H		H	H	4.5	519.3
1041		H	H		H	4.1	517.2 / 519.2
1042		H	H		H	4.2	517.2 / 519.2
1043		H	H		H	4.1	517.2 / 519.2

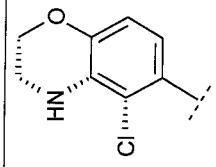
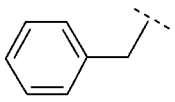
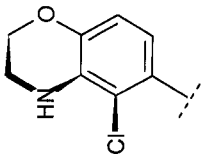
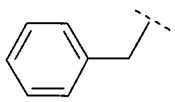
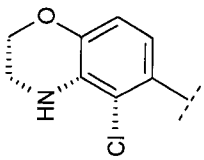
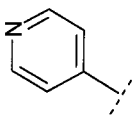
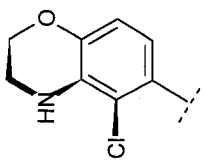
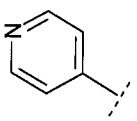
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1044		H	H		H	4.2	517.2 / 519.2
1045		H	H	H	$-CH_2CH_3$	5.4	434.3
1046		H	Br	H	$-CH_2CH_3$	7.1	512.2 / 514.2
1047		H	H		H	4.8	518.2 / 520.2

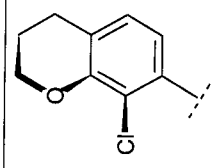
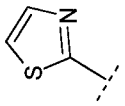
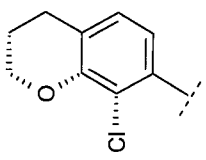
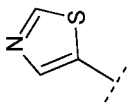
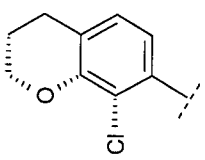
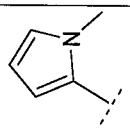
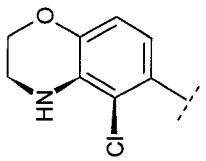
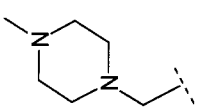
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1048		H	H		H	4.8	518.2 / 520.2
1049		H	H		H	5.9	516.2 / 518.2
1050		H	H		H	6.0	516.2 / 518.2
1051		H	Br	H	$-OCF_3$	8.2	568.1 / 570.1

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1052		H	H	H	$-CH_3$	5.0	420.3
1053		H	H		H	5.5	523.2 / 525.2
1054		H	H		H	5.0	523.2 / 525.2
1055		H	H		H	5.5	519.2 / 521.2

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1056		H	H	H		5.3	517.2 / 519.2
1057		H	H	H		5.5	517.2 / 519.2
1058		H	H	H		5.3	547.2 / 549.2
1059		H	H	H		5.6	547.2 / 549.2

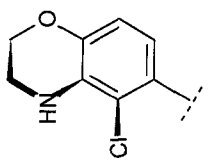
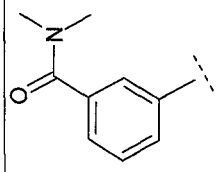
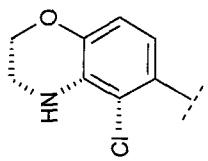
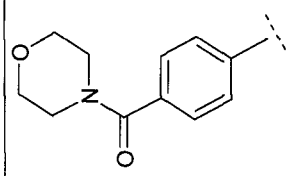
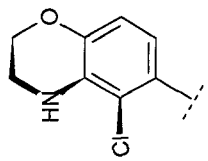
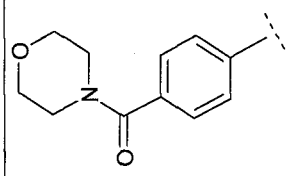
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1060		H	H	H		5.3	547.2 / 549.2
1061		H	H	H		5.5	547.2 / 549.2
1062		H	H	H		4.3	518.2 / 520.2
1063		H	H	H		4.6	518.2 / 520.2

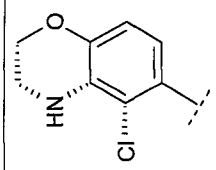
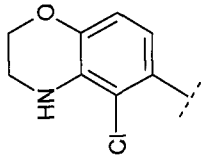
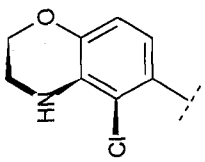
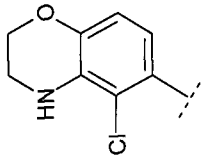
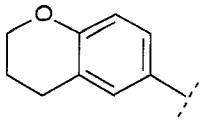
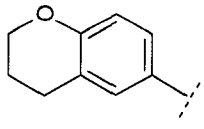
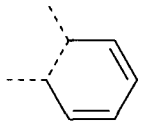
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1064		H	H	H		5.9	531.2 / 533.2
1065		H	H	H		6.1	531.2 / 533.2
1066		H	H	H		4.3	518.2 / 520.2
1067		H	H	H		4.5	518.2 / 520.2

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1068		H	H		H	5.4	523.2 / 525.2
1069		H	H		H	5.1	523.2 / 525.2
1070		H	H		H	5.7	519.3 / 521.2
1071		H	H		H	3.5	553.3 / 555.3

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1072		H	H	H	Br	5.6	519.1 / 521.1
1073		H	H	H	Br	6.0	519.1 / 521.1
1074		H	H		H	3.5	539.3 / 541.3
1075		H	H	H		4.8	610.1 / 612.1

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1076		H	H	H		5.1	610.1 / 612.1
1077		H	H	H		4.5	560.2 / 562.2
1078		H	H	H		4.7	560.2 / 562.2
1079		H	H	H		4.8	588.2 / 590.2

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1080		H	H	H		5.1	588.2 / 590.2
1081		H	H	H		4.8	630.2 / 632.2
1082		H	H	H		5.0	630.2 / 632.2

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1083		H	H	H		5.3	608.2 / 610.2 / 612.2
1084		H	H	H		5.5	608.2 / 610.2 / 612.2
1085		H	H	H	OCF_3	6.3	490.2
1086		H	H	H		6.0	456.2

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1087		H	H	H		5.0	467.2 / 469.2
1088		H	H	H		4.8	469.2 / 471.2
1089		H	H	H		4.6	507.2 / 509.1
1090		F	H	H	H	5.7	420.1 / 422.1

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1091		F	H	H	H	3.8	461.2
1092		H	H	Me	Cl	5.0	491.2 / 493.2
1093		H	F	Me	H	2.9	475.1
1094		H	H	CN	H	4.3	468.0
1095		H	H	CN	H	5.5	431.1

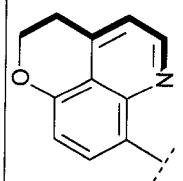
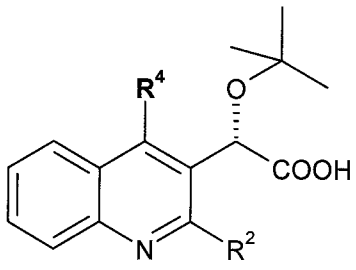
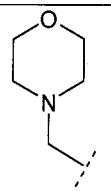
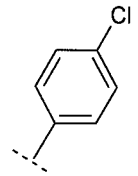
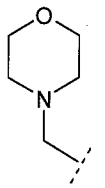
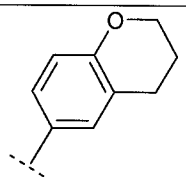
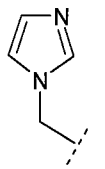
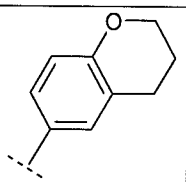
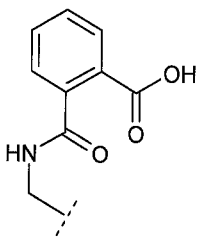
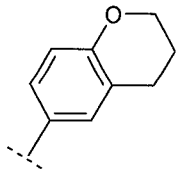
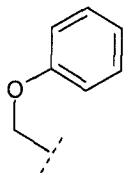
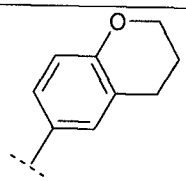
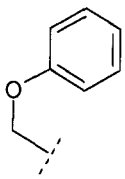
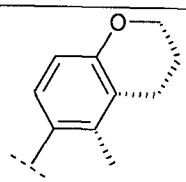
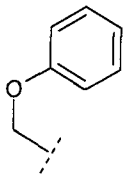
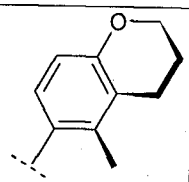
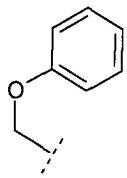
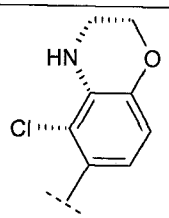
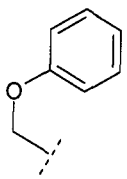
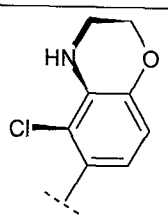
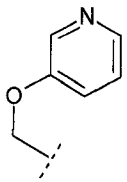
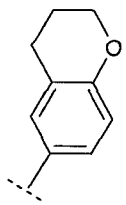
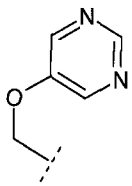
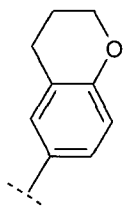
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
1096		H	H	-C(=O)-NH-t-Bu	H	4.3	542.1

TABLE 2



Cpd	R^2	R^4	t_R (min)	MS $(M+H)^+$
2001			5.1	469.3 / 471.3
2002			5.0	491.4
2003			5.0	472.4
2004			5.2	569.3

Cpd	R^2	R^4	t_R (min)	MS $(M+H)^+$
2005			6.6	498.3
2006			6.8	512.3
2007			6.8	512.3
2008			6.5	533.2 / 535.2
2009			6.7	533.2 / 535.2
2010			5.0	499.4
2011			6.0	500.3

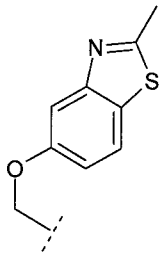
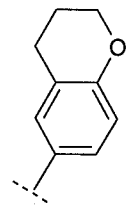
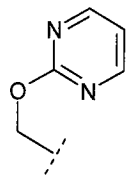
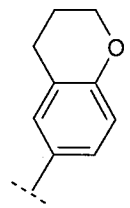
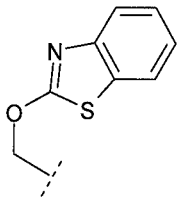
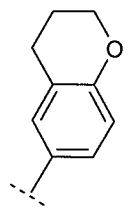
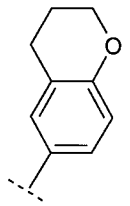
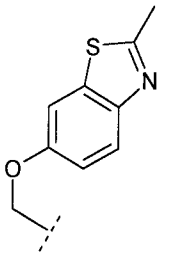
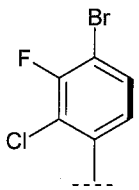
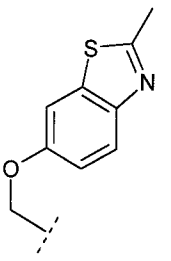
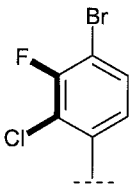
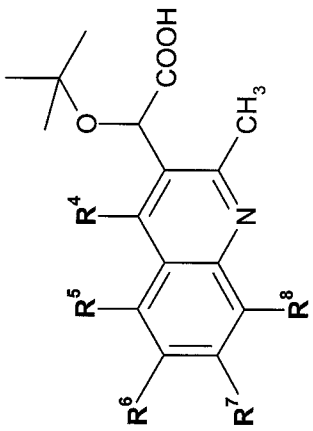
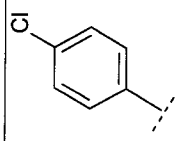
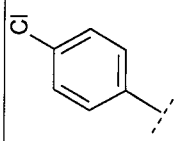
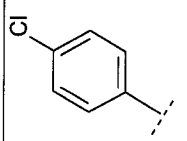
Cpd	R^2	R^4	t_R (min)	MS $(M+H)^+$
2012			6.7	569.3
2013			5.5	500.3
2014			8.3	555.2
2015	-CH_2OCH_3		4.8	436.2
2016			8.2	643.0 / 645.0 / 647.0
2017			8.1	643.0 / 645.0 / 647.0

TABLE 3



Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
3001		F	H	H	H	4.7	402.0
3002		H	H	H	F	5.2	402.1
3003		$-OCH_3$	H	H	H	4.5	414.2 / 416.2

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
3004		H	$-OCH_3$	H	H	4.6	414.1 / 416.1
3005		H	H	$-OCH_3$	H	4.6	414.1 / 416.1
3006		H	H	H	$-OCH_3$	4.5	414.1 / 416.1
3007		H	H	H	$-CH_3$	4.7	398.1 / 400.1
3008		H	H	$-CH=CH_2$	H	4.9	410.2 / 412.2

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
3009		H	H		H	5.2	424.2 / 426.2
3010		F	H	H	H	5.0	424.2
3011		H	H	$-NO_2$	H	7.5	429.1 / 431.1
3012		H	H	$-NH_2$	H	5.2	399.1 / 401.1
3013		H	H	$-CH_2OH$	H	4.9	414.1 / 416.1

Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
3014		H	H	$-C(=O)NH_2$	H	4.7	427.1 / 429.1
3015		H	H	-CN	H	6.5	409.1 / 411.1
3016		H	H	$-NHC(=O)CH_3$	H	5.0	441.1 / 443.1
3017		$-CH_3$	H	H	H	4.0	398.3
3018		$-CH_3$	H	H	H	4.0	420.4

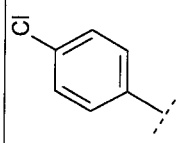
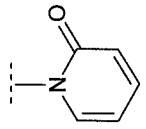
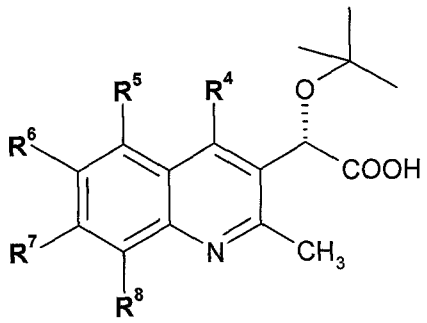
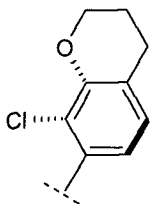
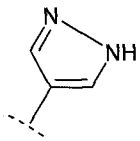
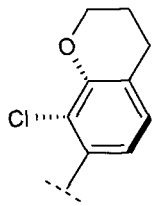
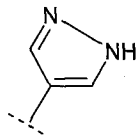
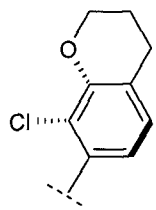
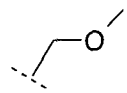
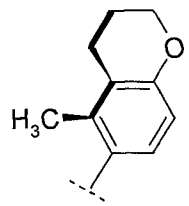
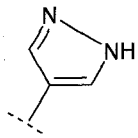
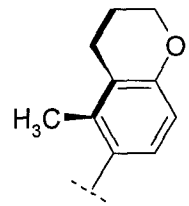
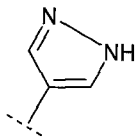
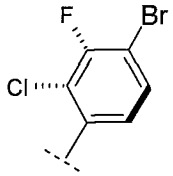
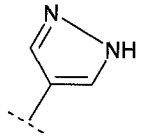
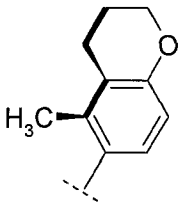
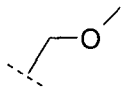
Cpd	R^4	R^5	R^6	R^7	R^8	t_R (min)	MS $(M+H)^+$
3019		H	H	H		5.3	477.2 / 479.2

TABLE 4



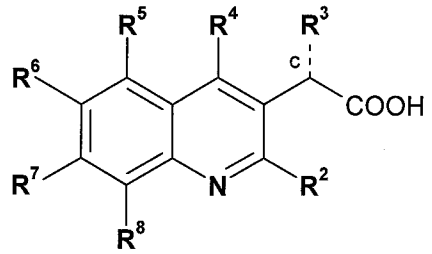
Cpd	R^4	R^5	R^6	R^7	R^8	R^2
4001		H	H	H		CH_3
4002		H	H		H	CH_3
4003		H	H	H	H	
4004		H	H	H		CH_3
4005		H	H		H	CH_3

Cpd	R^4	R^5	R^6	R^7	R^8	R^2
4006		H	H	H		CH_3
4007		H	H	H	H	

All of the documents cited herein are incorporated in to the invention as a reference, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

CLAIMS

1. An isomer, racemate, enantiomer or diastereomer of a compound of formula (I):



(I)

wherein

R^2 is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl, **Het**, halo, nitro or cyano;

b) $-C(=O)-R^{11}$, $-C(=O)-O-R^{11}$, $-S-R^{11}$, $-SO-R^{11}$, $-SO_2-R^{11}$, $-(C_{1-6})$alkylene-R^{11}, $-(C_{1-6})$alkylene-$C(=O)-R^{11}$, $-(C_{1-6})$alkylene-$C(=O)-O-R^{11}$, $-(C_{1-6})$alkylene-$O-R^{11}$, $-(C_{1-6})$alkylene-$S-R^{11}$, $-(C_{1-6})$alkylene-$SO-R^{11}$ or $-(C_{1-6})$alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, $-O(C_{1-6})$alkyl, $-O(C_{1-6})$haloalkyl, -SH, $-S(C_{1-6})$alkyl, $-SO(C_{1-6})$alkyl, $-SO_2(C_{1-6})$alkyl, $-C(=O)-NH_2$, $-C(=O)-NH(C_{1-4})$alkyl, $-C(=O)-N((C_{1-4})alkyl)_2$, -C(=O)-aryl, --C(=O)-**Het**, NH_2, $-NH(C_{1-6})$alkyl and $-N((C_{1-6})alkyl)_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, $-O-(C_{1-6})$haloalkyl, or $-O-(C_{1-6})$alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

c) -O-R^{8a}

wherein R^{8a} is selected from H, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

d) -N(R^9)R^{10}, –C(=O)-N(R^9)R^{10}, –O-C(=O)-N(R^9)R^{10}, –SO_2-N(R^9)R^{10}, -(C_{1-6})alkylene-N(R^9)R^{10}, -(C_{1-6})alkylene-C(=O)-N(R^9)R^{10}, -(C_{1-6})alkylene–O-C(=O)-N(R^9)R^{10}, or -(C_{1-6})alkylene-SO_2-N(R^9)R^{10}

wherein

R^9 is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

R^{10} is in each instance independently selected from R^{11}, -(C_{1-6})alkylene-R^{11}, -SO_2-R^{11}, -C(=O)-R^{11}, -C(=O)OR^{11} and -C(=O)N(R^9)R^{11}; wherein R^{11} and R^9 are as defined above; or

R^2 may also be H, (C_{1-6})alkyl or -O-(C_{1-6})alkyl when one of R^5 or R^8 is other than H or when one of R^6 or R^7 is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl,

R^5 and R^8 are each independently selected from:

a) halo, nitro or cyano;

b) R^{11}, -C(=O)-R^{11}, -C(=O)-O-R^{11}, -O-R^{11}, -S-R^{11}, -SO-R^{11}, -SO_2-R^{11}, -(C_{1-6})alkylene-R^{11}, -(C_{1-6})alkylene-C(=O)-R^{11}, -(C_{1-6})alkylene-C(=O)-O-R^{11}, -(C_{1-6})alkylene-O-R^{11}, –(C_{1-6})alkylene-S-R^{11}, -(C_{1-6})alkylene-SO-R^{11} or -(C_{1-6})alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -SO_2(C_{1-6})alkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N((C_{1-4})alkyl)$_2$, -C(=O)-aryl, -C(=O)-**Het**, NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

c) $-N(\mathbf{R^9})\mathbf{R^{10}}$, $-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-O-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-SO_2-N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene-$N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene-$C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene$-O-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, or $-(C_{1-6})$alkylene-$SO_2-N(\mathbf{R^9})\mathbf{R^{10}}$ wherein

$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$\mathbf{R^{11}}$, $-SO_2-\mathbf{R^{11}}$, $-C(=O)-\mathbf{R^{11}}$, $-C(=O)O\mathbf{R^{11}}$ and $-C(=O)N(\mathbf{R^9})\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above;

$\mathbf{R^6}$ is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) $-C(=O)-\mathbf{R^{11}}$, $-C(=O)-O-\mathbf{R^{11}}$, $-O-\mathbf{R^{11}}$, $-S-\mathbf{R^{11}}$, $-SO-\mathbf{R^{11}}$, $-SO_2-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$C(=O)-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$C(=O)-O-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$O-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$S-\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$SO-\mathbf{R^{11}}$ or $-(C_{1-6})$alkylene-$SO_2-\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

c) $-N(\mathbf{R^9})\mathbf{R^{10}}$, $-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-O-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-SO_2-N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene-$N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene-$C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, $-(C_{1-6})$alkylene$-O-C(=O)-N(\mathbf{R^9})\mathbf{R^{10}}$, or $-(C_{1-6})$alkylene-$SO_2-N(\mathbf{R^9})\mathbf{R^{10}}$ wherein

$\mathbf{R^9}$ is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$\mathbf{R^{11}}$, $-SO_2-\mathbf{R^{11}}$, $-C(=O)-\mathbf{R^{11}}$, $-C(=O)O\mathbf{R^{11}}$ and $-C(=O)N(\mathbf{R^9})\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, $-O(C_{1-6})$alkyl,

-O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -SO_2(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

R^6 may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl;

R^7 is selected from:

a) (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) -C(=O)-R^{11}, -C(=O)-O-R^{11}, -O-R^{11}, -S-R^{11}, -SO-R^{11}, -SO_2-R^{11}, -(C_{1-6})alkylene-R^{11}, -(C_{1-6})alkylene-C(=O)-R^{11}, -(C_{1-6})alkylene-C(=O)-O-R^{11}, -(C_{1-6})alkylene-O-R^{11}, –(C_{1-6})alkylene-S-R^{11}, -(C_{1-6})alkylene-SO-R^{11} or -(C_{1-6})alkylene-SO_2-R^{11}; wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**;

and

c) -N(R^9)R^{10}, –C(=O)-N(R^9)R^{10}, –O-C(=O)-N(R^9)R^{10}, –SO_2-N(R^9)R^{10}, -(C_{1-6})alkylene-N(R^9)R^{10}, -(C_{1-6})alkylene-C(=O)-N(R^9)R^{10}, -(C_{1-6})alkylene–O-C(=O)-N(R^9)R^{10}, or -(C_{1-6})alkylene-SO_2-N(R^9)R^{10} wherein

R^9 is in each instance independently selected from H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl; and

R^{10} is in each instance independently selected from R^{11}, -(C_{1-6})alkylene-R^{11}, -SO_2-R^{11}, -C(=O)-R^{11}, -C(=O)OR^{11} and -C(=O)N(R^9)R^{11}; wherein R^{11} and R^9 are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, -O(C_{1-6})alkyl, -O(C_{1-6})haloalkyl, -SH, -S(C_{1-6})alkyl, -SO(C_{1-6})alkyl, -SO_2(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, -O-(C_{1-6})haloalkyl, or -O-(C_{1-6})alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH; and

R^7 may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of R^5 or R^8 is other than H or when R^6 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl;

or R^5 and R^6, together with the C to which they are attached, R^6 and R^7, together with the C to which they are attached, or R^7 and R^8, together with the C to which they are attached; may be linked to form a 5- or 6-membered carbocycle or a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2;

wherein the carbocycle or heterocycle is optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})$alkyl$)_2$;

R^3 is (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl-, **Het**-(C_{1-6})alkyl- or -**Y**-R^{31}, and bond **c** is a single bond; or

R^3 is (C_{1-6})alkylidene and bond **c** is a double bond;

wherein **Y** is O or S and R^{31} is (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, aryl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl- or **Het**-(C_{1-6})alkyl-;

wherein each of the (C_{1-6})alkylidene, (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-6})alkyl-, **Het**-(C_{1-6})alkyl- and -**Y**-R^{31} is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, halo, cyano, oxo and -O(C_{1-6})alkyl;

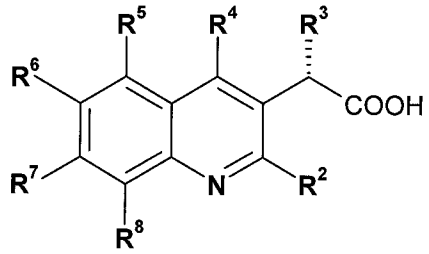
R^4 is aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with 1 to 5 substituents each independently selected from halo, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, -OH, -O(C_{1-6})alkyl, -SH, -S(C_{1-6})alkyl, $-NH_2$,

-NH(C_{1-6})alkyl and -N((C_{1-6})alkyl)$_2$; wherein the (C_{1-6})alkyl is optionally substituted with hydroxy, -O(C_{1-6})alkyl, cyano or oxo;

wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2;

or a salt or an ester thereof.

2. The compound according to claim 1, of formula (Ib):



(Ib)

Wherein $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ are as defined in claim 1.

3. The compound according to claim 1 and 2, wherein $\mathbf{R^2}$ is selected from H, (C_{1-6})alkyl or -O-(C_{1-6})alkyl when one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when one of $\mathbf{R^6}$ or $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

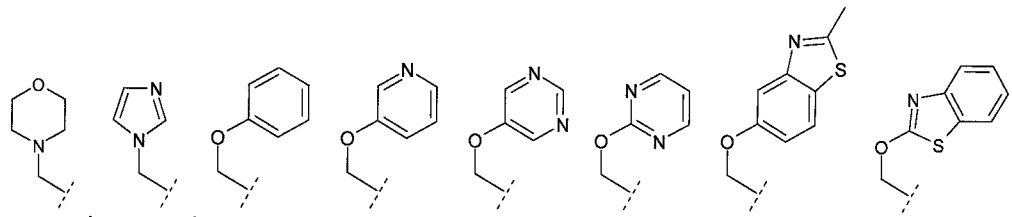
4. The compound according to claim 3, wherein $\mathbf{R^2}$ is selected from (C_{1-6})alkyl when one of $\mathbf{R^5}$ and $\mathbf{R^8}$ is other than H or when one of $\mathbf{R^6}$ or $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

5. The compound according to claim 4, wherein $\mathbf{R^2}$ is selected from -CH_3 or -CH_2CH_3 when one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when one of $\mathbf{R^6}$ or $\mathbf{R^7}$ is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

6. The compound according to claims 1 and 2, wherein R^2 is selected from -(C_{1-6})alkylene-**Het**, -(C_{1-6})alkylene-aryl, -(C_{1-6})alkylene-O-**Het**, -(C_{1-6})alkylene-O-aryl, **Het** or aryl, all being optionally substituted with (C_{1-6})alkyl, (C_{1-6})haloalkyl, or -O(C_{1-6})alkyl.

7. The compound according to claim 1 or 2, wherein R^2 is selected from -(C_{1-6})alkylene-**Het**, -(C_{1-6})alkylene-aryl, -(C_{1-6})alkylene-O-**Het** or -(C_{1-6})alkylene-O-aryl; or
(C_{1-6})alkyl, when one of R^5 or R^8 is other than H or when one of R^6 or R^7 is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

8. The compound according to claim 7, wherein R^2 is selected from:



; or CH_3, when one of R^5 or R^8 is other than H or when one of R^6 or R^7 is other than H, halo, (C_{1-6})alkyl or (C_{1-6})haloalkyl.

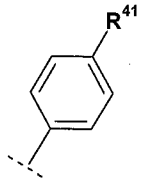
9. The compound according to any one of claims 1 to 8, wherein R^3 is selected from -O(C_{1-6})alkyl, -O-(C_{1-6})haloalkyl, -O(C_{2-6})alkenyl, -O(C_{2-6})alkynyl or -O-(C_{3-7})cycloalkyl;
wherein each of the -O(C_{1-6})alkyl and -O-(C_{3-7})cycloalkyl is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-3})alkyl, cyano, oxo and -O(C_{1-6})alkyl; and
bond **c** is a single bond.

10. The compound according to claim 9, wherein R^3 is selected from –OC(CH_3)$_3$; and bond **c** is a single bond.

11. The compound according to any one of claims 1 to 10, wherein R^4 is selected from phenyl optionally substituted with 1 to 3 substituents each independently

selected from halo, (C_{1-4})alkyl and (C_{1-4})haloalkyl.

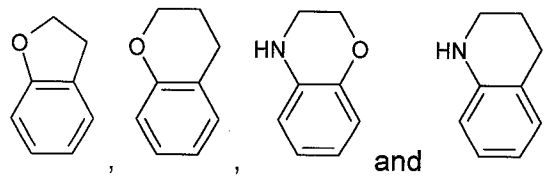
12. The compound according to claim 11, wherein $\mathbf{R^4}$ is a group of formula:



wherein $\mathbf{R^{41}}$ is selected from halo, (C_{1-4})alkyl and (C_{1-4})haloalkyl.

13. The compound according to any one of claims 1 to 10, wherein $\mathbf{R^4}$ is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo and (C_{1-6})alkyl;
wherein the **Het** is a 5- or 6-membered heterocycle having 1 to 3 heteroatoms each independently selected from N, O and S; or the **Het** is a 9- or 10-membered heteropolycycle having 1 to 3 heteroatoms each independently selected from N, O and S.

14. The compound according to claim any one of claims 1 to 10, wherein $\mathbf{R^4}$ is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, (C_{1-6})alkyl and $-O(C_{1-6})$alkyl;
wherein the Het is selected from:



, , and .

15. The compound according to any one of claims 1 to 14, wherein $\mathbf{R^5}$ is H, halo, (C_{1-6})alkyl, (C_{1-6})haloalkyl or $-O(C_{1-6})$alkyl.

16. The compound according to claim 15, wherein $\mathbf{R^5}$ is H, halo or (C_{1-4})alkyl.

17. The compound according to claim 16, wherein $\mathbf{R^5}$ is H, F or CH_3.

18. The compound according to claim 17, wherein $\mathbf{R^5}$ is F or H.

19. The compound according to any one of claims 1 to 18, wherein R^6 is selected from:

a) (C_{2-6})alkenyl, aryl and **Het**; and

b) -O-(C_{1-6})alkyl; or

R^6 may also be halo when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

20. The compound according to any one of claims 1 to 18, wherein R^6 is $CH=CH_2$, phenyl, OCH_3; or

CH_3, CH_2CH_3, H, F, Cl or Br when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

21. The compound according to claim 20, wherein R^6 is H when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

22. The compound according to any one of claims 1 to 18, wherein R^6 is C≡CH, $CH=CH_2$, phenyl or OCH_3; or

H, Br when at least one of R^5 or R^8 is other than H or when R^7 is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when R^2 is other than H, (C_{1-6})alkyl, or –O-(C_{1-6})alkyl.

23. The compound according to any one of claims 1 to 22, wherein R^7 is selected from:

a) (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, nitro, cyano, aryl and **Het**;

b) -(C_{1-6})alkylene-R^{11},

wherein R^{11} is in each instance independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, aryl and **Het**; and

c) $-N(R^9)R^{10}$, $-C(=O)-N(R^9)R^{10}$, wherein

R^9 is in each instance independently selected from H, (C_{1-6})alkyl and

(C_{3-7})cycloalkyl; and

$\mathbf{R^{10}}$ is in each instance independently selected from $\mathbf{R^{11}}$, $-(C_{1-6})$alkylene-$\mathbf{R^{11}}$, $-SO_2-\mathbf{R^{11}}$, $-C(=O)-\mathbf{R^{11}}$, $-C(=O)O\mathbf{R^{11}}$ and $-C(=O)N(\mathbf{R^9})\mathbf{R^{11}}$; wherein $\mathbf{R^{11}}$ and $\mathbf{R^9}$ are as defined above;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

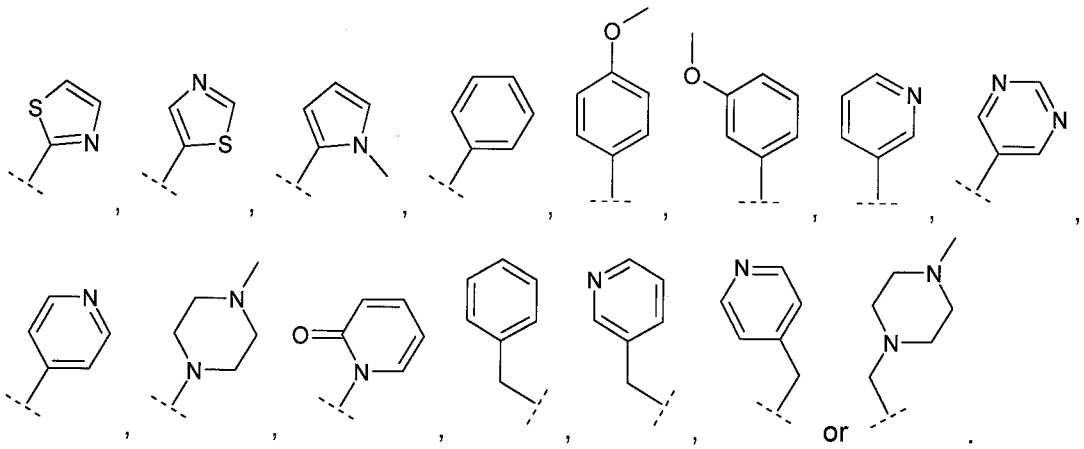
i) halo, oxo, thioxo, (C_{2-6})alkenyl, (C_{1-6})haloalkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, -OH, $-O(C_{1-6})$alkyl, $-O(C_{1-6})$haloalkyl, -SH, $-S(C_{1-6})$alkyl, $-SO(C_{1-6})$alkyl, $-SO_2(C_{1-6})$alkyl, $-NH_2$, $-NH(C_{1-6})$alkyl and $-N((C_{1-6})\text{alkyl})_2$;

ii) (C_{1-6})alkyl optionally substituted with –OH, $-O-(C_{1-6})$haloalkyl, or $-O-(C_{1-6})$alkyl; and

iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo, (C_{1-6})alkyl or COOH;

$\mathbf{R^7}$ may also be H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl when at least one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when $\mathbf{R^6}$ is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when $\mathbf{R^2}$ is other than H, (C_{1-6})alkyl, or $-O-(C_{1-6})$alkyl.

24. The compound according to anyone of claims 1 to 22, wherein $\mathbf{R^7}$ is CH_2OH, CN, OCH_3, $CH=CH_2$, cyclopropyl, NH_2, NO_2, $CONH_2$, $NHC(=O)CH_3$,



25. The compound according to claims 23 and 24, wherein $\mathbf{R^7}$ is H, when at least one of $\mathbf{R^5}$ or $\mathbf{R^8}$ is other than H or when $\mathbf{R^6}$ is other than H, halo, (C_{1-6})alkyl, or (C_{1-6})haloalkyl or when $\mathbf{R^2}$ is other than H, (C_{1-6})alkyl, or $-O-(C_{1-6})$alkyl.

26. The compound according to any one of claims 1 to 25, wherein $\mathbf{R^8}$ is selected

from:

a) halo; and

b) H, (C_{1-6})alkyl, (C_{1-6})haloalkyl, -O-(C_{1-6})haloalkyl, aryl and **Het**, -(C_{1-6})alkylene-aryl, -(C_{1-6})alkylene-**Het**;

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

i) halo, oxo, thioxo, -O(C_{1-6})alkyl, -O (C_{1-6})haloalkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N$((C_{1-4})alkyl)_2$, -C(=O)-aryl, --C(=O)-**Het**; and

ii) (C_{1-6})alkyl.

27. The compound according to claim 26, wherein $\mathbf{R^8}$ is selected from:

a) F, Cl, Br; and

b) H, (C_{1-3})alkyl, , -O-(C_{1-3})haloalkyl, phenyl and **Het**, -(C_{1-3})alkylene-phenyl, -(C_{1-3})alkylene-**Het**;

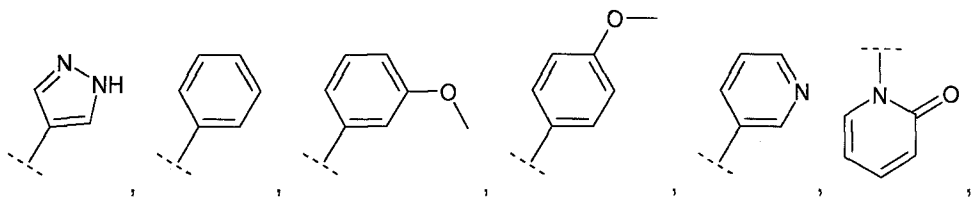
wherein each of the aryl and **Het** is optionally substituted with 1 to 2 substituents each independently selected from:

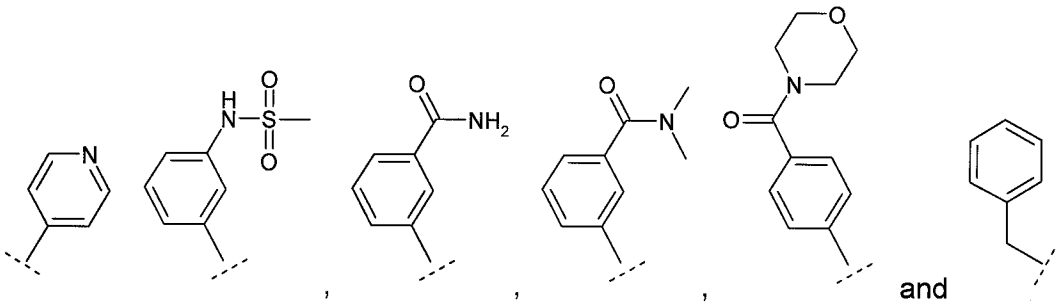
i) oxo, thioxo, -O(C_{1-6})alkyl, -C(=O)-NH_2, -C(=O)-NH(C_{1-4})alkyl, -C(=O)-N$((C_{1-4})alkyl)_2$, -C(=O)-aryl, --C(=O)-**Het**; and

ii) (C_{1-6})alkyl.

28. The compound according to claim 27, wherein $\mathbf{R^8}$ is H, Br, F, CH_3, CH_2CH_3 or OCF_3.

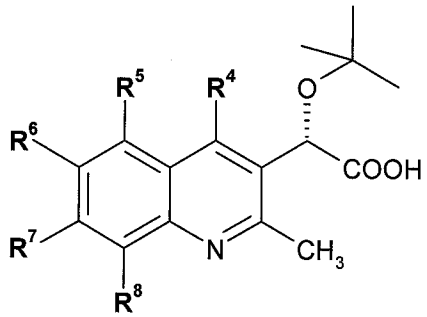
29. The compound according to claim 27, wherein $\mathbf{R^8}$ is selected from:



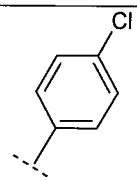
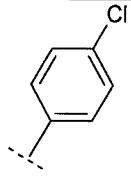
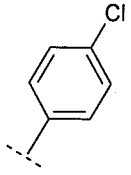
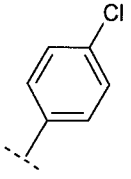


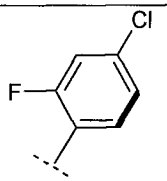
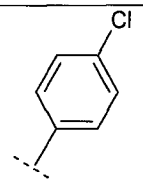
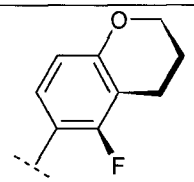
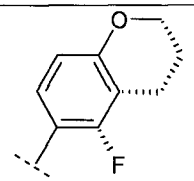
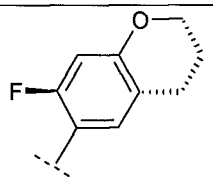
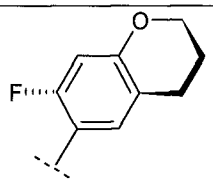
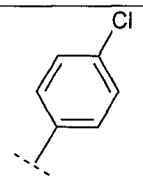
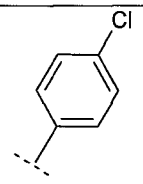
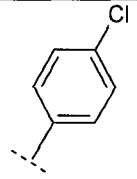
and .

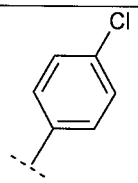
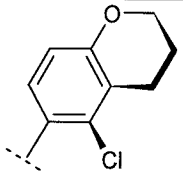
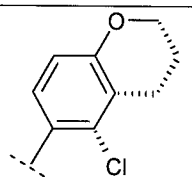
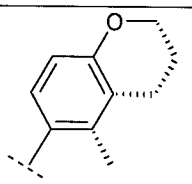
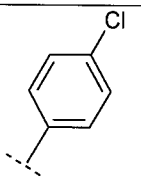
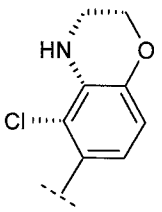
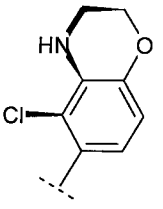
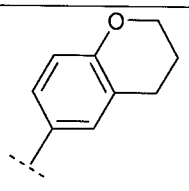
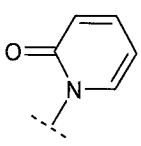
30. A compound according to claim 1 and 2 having the formula:

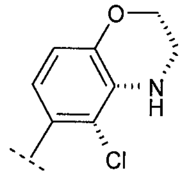
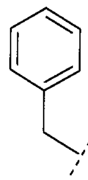
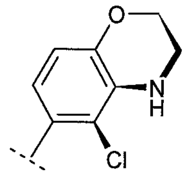
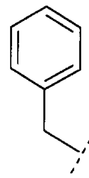
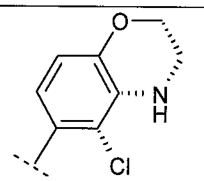
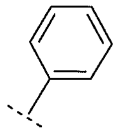
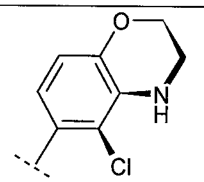
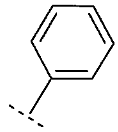
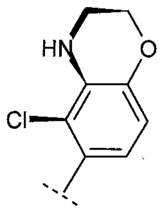
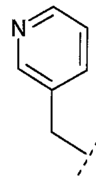
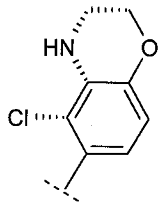
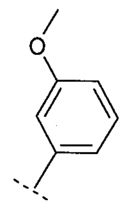
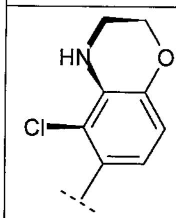
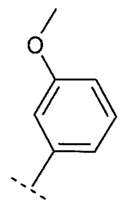
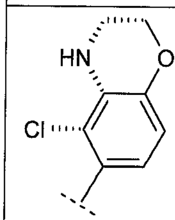
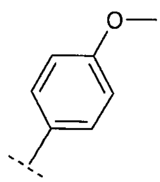


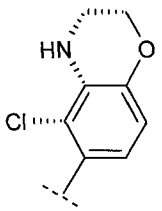
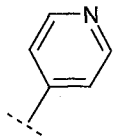
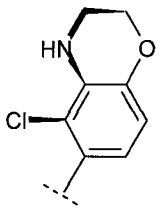
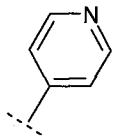
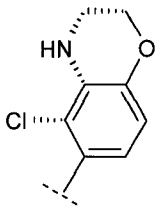
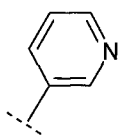
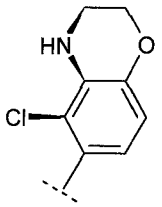
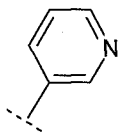
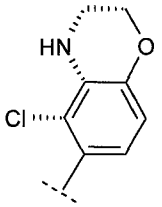
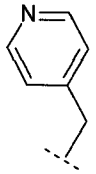
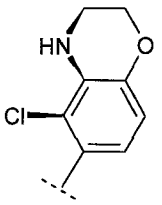
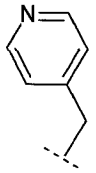
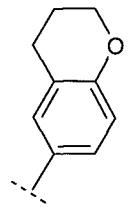
wherein **R^4, R^5, R^6, R^7 and R^8** are defined according to the following table:

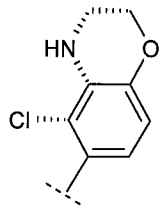
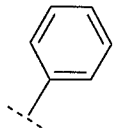
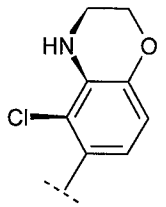
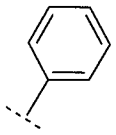
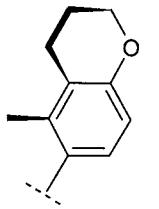
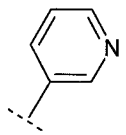
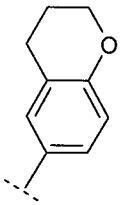
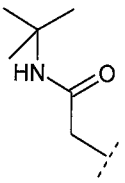
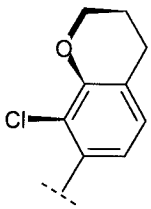
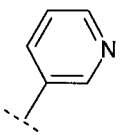
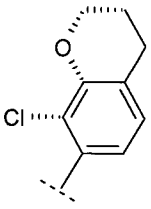
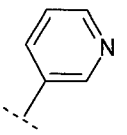
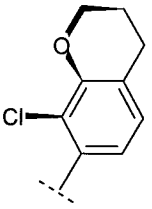
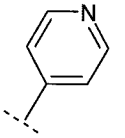
R^4	R^5	R^6	R^7	R^8	
	F	H	H	H	;
	H	$-OCH_3$	H	H	;
	H	H	$-OCH_3$	H	;
	H	H	H	F	;

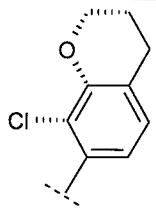
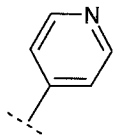
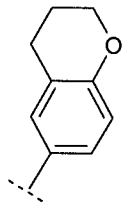
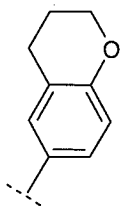
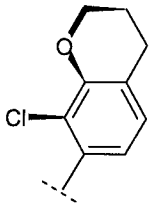
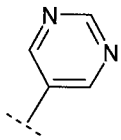
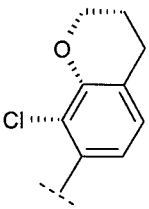
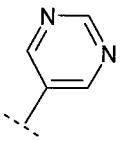
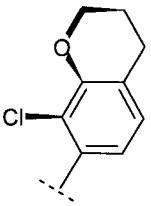
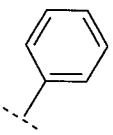
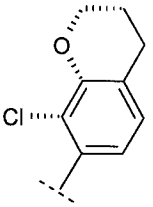
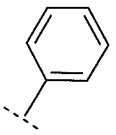
R^4	R^5	R^6	R^7	R^8	
	F	H	H	H	;
	H	-CH=CH$_2$	H	H	;
	F	H	H	H	;
	F	H	H	H	;
	F	H	H	H	;
	F	H	H	H	;
	H	-CN	H	H	;
	H	-C(=O)H	H	H	;
	H	-CH$_2$OH	H	H	;

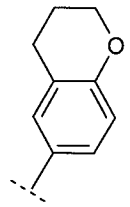
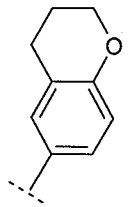
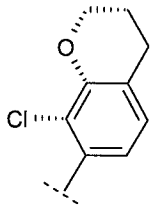
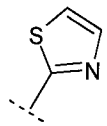
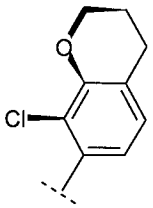
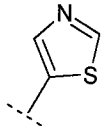
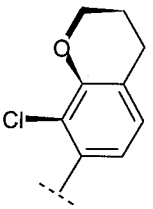
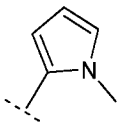
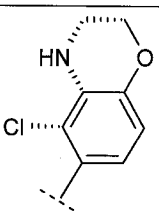
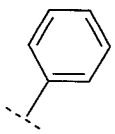
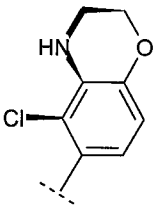
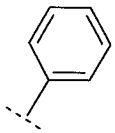
R^4	R^5	R^6	R^7	R^8	
	H	-C≡CH	H	H	;
	F	H	H	H	;
	F	H	H	H	;
	F	H	H	H	;
	H	H	H	Br	;
	F	H	H	H	;
	F	H	H	H	;
	H	H		H	;

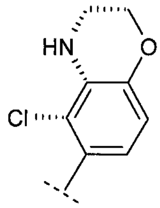
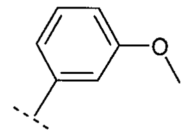
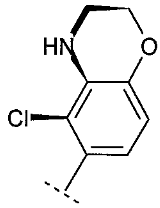
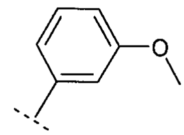
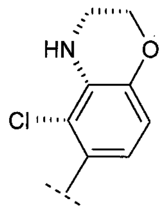
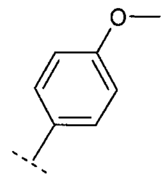
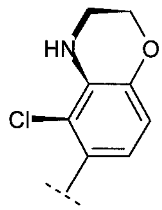
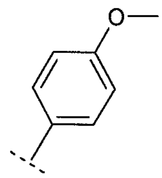
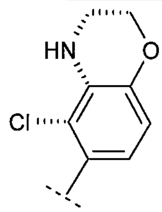
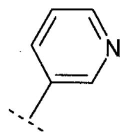
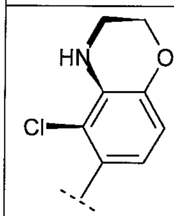
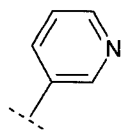
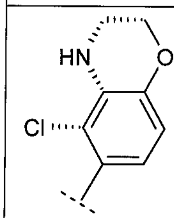
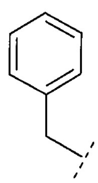
R^4	R^5	R^6	R^7	R^8	
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;

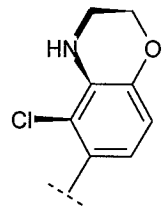
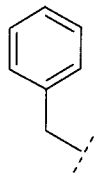
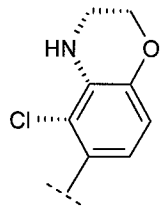
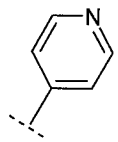
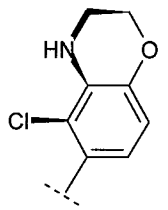
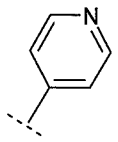
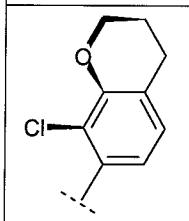
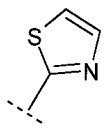
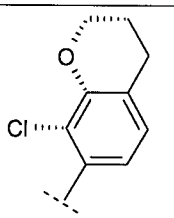
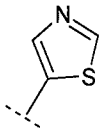
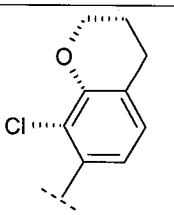
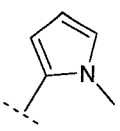
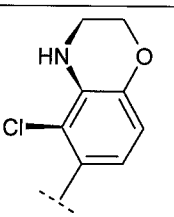
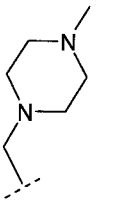
R^4	R^5	R^6	R^7	R^8	
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	Br	H	$-CH_3$	;

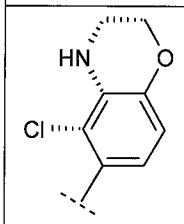
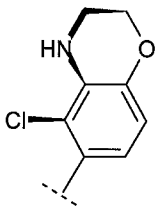
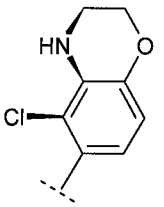
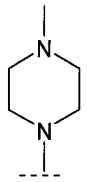
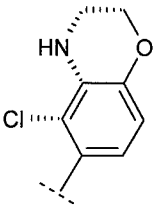
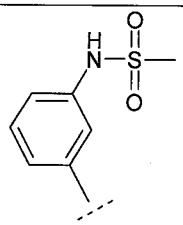
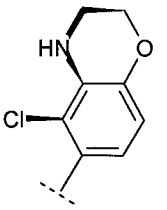
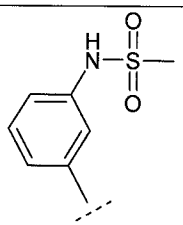
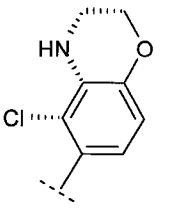
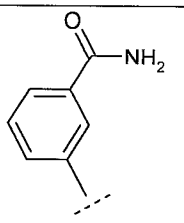
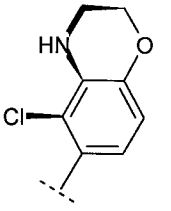
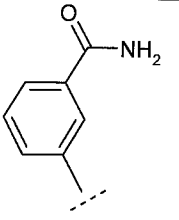
R^4	R^5	R^6	R^7	R^8	
	H		H	H	;
	H		H	H	;
	H	H		H	;
	H		H	H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;

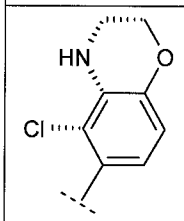
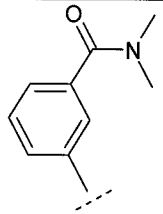
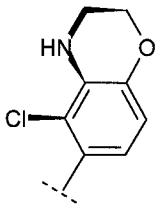
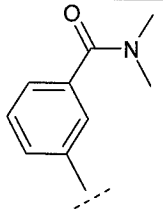
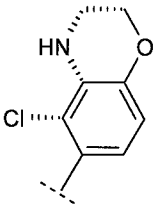
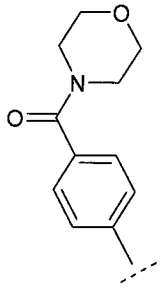
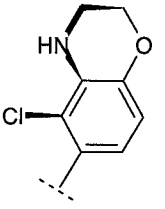
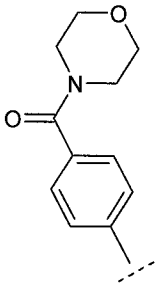
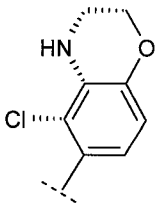
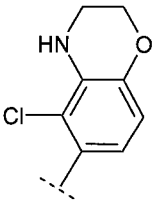
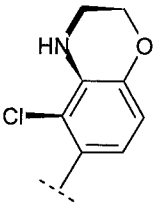
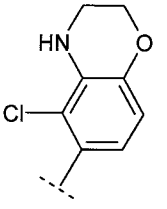
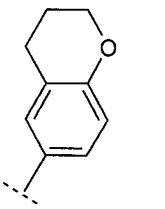
R^4	R^5	R^6	R^7	R^8	
	H	H		H	;
	H	H	H	$-CH_2CH_3$	;
	H	Br	H	$-CH_2CH_3$	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;

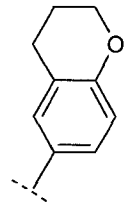
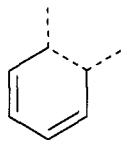
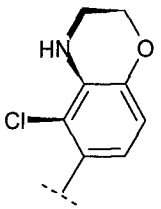
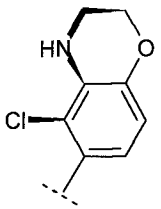
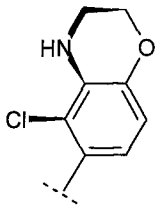
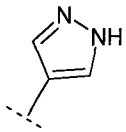
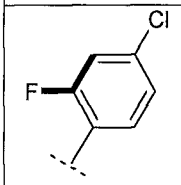
R^4	R^5	R^6	R^7	R^8	
	H	Br	H	$-OCF_3$	;
	H	H	H	$-CH_3$	;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H	H		;
	H	H	H		;

R⁴	R⁵	R⁶	R⁷	R⁸	
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H		;

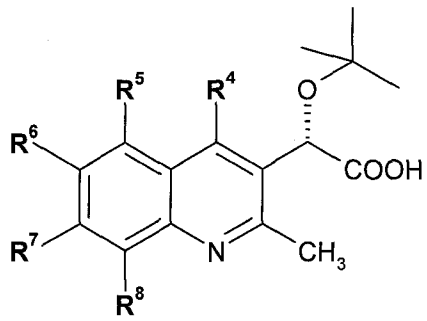
R^4	R^5	R^6	R^7	R^8	
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H		H	;
	H	H		H	;
	H	H		H	;
	H	H		H	;

R^4	R^5	R^6	R^7	R^8	
	H	H	H	Br	;
	H	H	H	Br	;
	H	H		H	;
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H		;

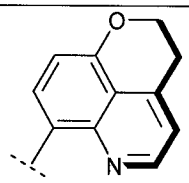
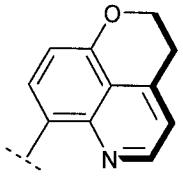
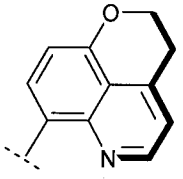
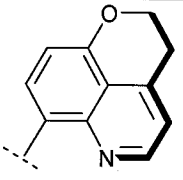
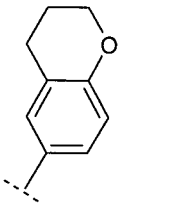
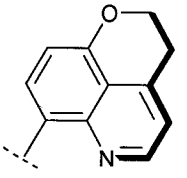
R^4	R^5	R^6	R^7	R^8	
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H		;
	H	H	H	OCF_3	;

R^4	R^5	R^6	R^7	R^8	
	H	H			;
	H	H	H		;
	H	H	H		;
	H	H	H		and
	F	H	H	H	.

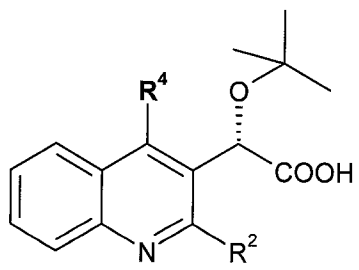
31. A compound according to claim 1 and 2 having the formula:



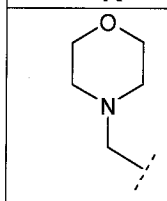
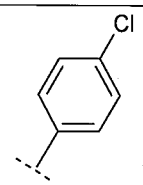
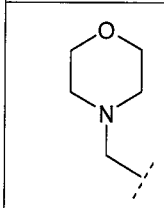
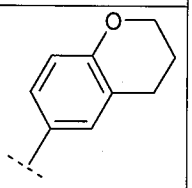
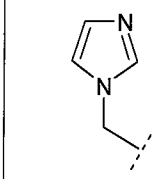
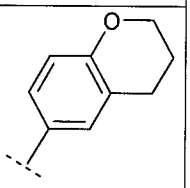
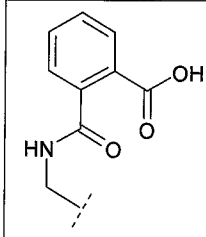
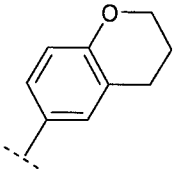
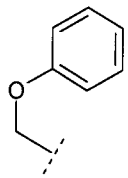
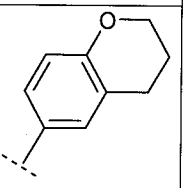
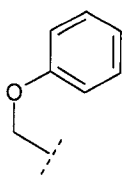
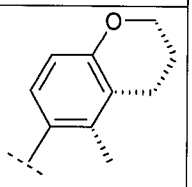
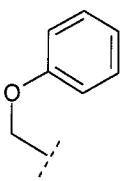
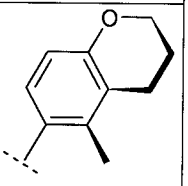
wherein R^4, R^5, R^6, R^7 **and** R^8 are defined according to the following table:

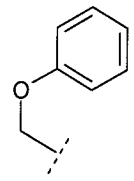
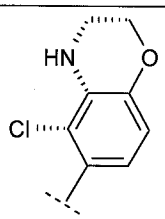
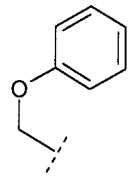
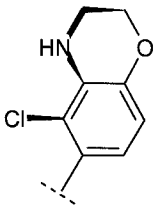
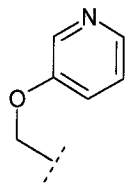
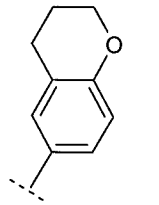
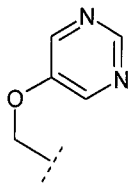
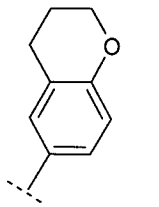
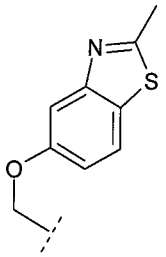
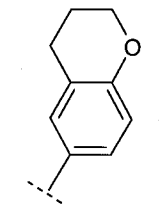
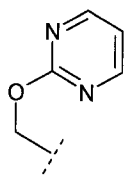
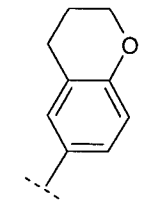
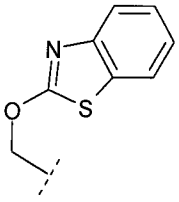
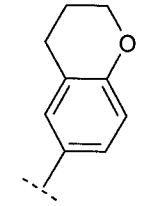
R^4	R^5	R^6	R^7	R^8	
	F	H	H	H	;
	H	H	Me	Cl	;
	H	F	Me	H	;
	H	H	CN	H	;
	H	H	CN	H	and
	H	H	-C(=O)-NH-t-Bu	H	.

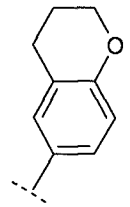
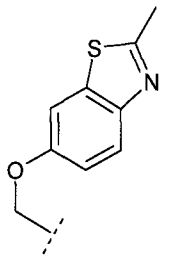
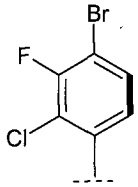
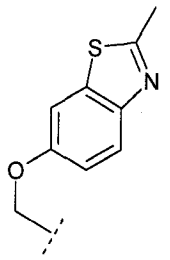
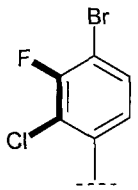
32. A compound according to claim 1 and 2 having the formula:



wherein R^2 and R^4 are defined according to the following table:

R^2	R^4
	 ;
	 ;
	 ;
	 ;
	 ;
	 ;
	 ;

R^2	R^4	
		;
		;
		;
		;
		;
		;
		;

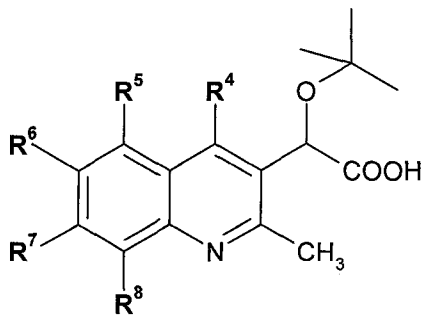
R^2	R^4
$-CH_2OCH_3$	
	
	

;

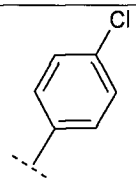
and

.

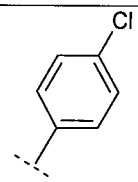
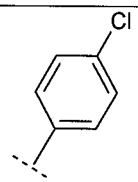
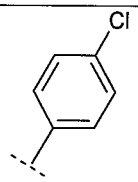
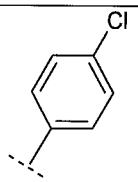
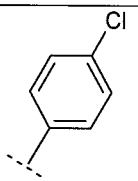
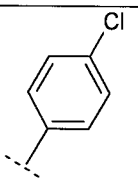
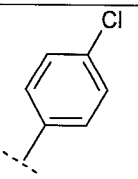
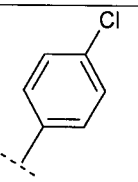
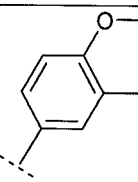
33. A compound according to claim 1 and 2 having the formula:

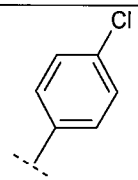
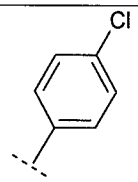
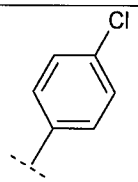
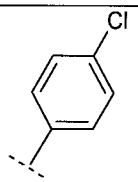
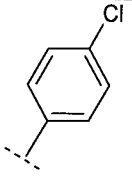
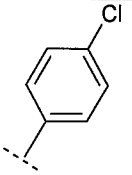
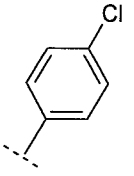
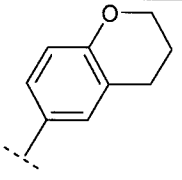
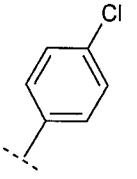
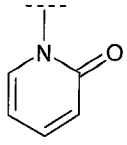


wherein R^4, R^5, R^6, R^7 **and** R^8 are defined according to the following table:

R^4	R^5	R^6	R^7	R^8
	F	H	H	H

;

R^4	R^5	R^6	R^7	R^8	
	H	H	H	F	;
	$-OCH_3$	H	H	H	;
	H	$-OCH_3$	H	H	;
	H	H	$-OCH_3$	H	;
	H	H	H	$-OCH_3$	;
	H	H	H	$-CH_3$	;
	H	H	$-CH=CH_2$	H	;
	H	H		H	;
	F	H	H	H	;

R^4	R^5	R^6	R^7	R^8	
	H	H	$-NO_2$	H	;
	H	H	$-NH_2$	H	;
	H	H	$-CH_2OH$	H	;
	H	H	$-C(=O)NH_2$	H	;
	H	H	-CN	H	;
	H	H	$-NHC(=O)CH_3$	H	;
	$-CH_3$	H	H	H	;
	$-CH_3$	H	H	H	and
	H	H	H		.

34. A compound of formula (I) according to any one of claims 1 to 33, or a pharmaceutically acceptable salt or ester thereof, as a medicament.

35. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 33, or a pharmaceutically acceptable salt or ester thereof; and one or more pharmaceutically acceptable carriers.

36. The pharmaceutical composition according to claim 35 comprising at least one other antiviral agent.

37. The pharmaceutical composition as defined in claim 36 wherein the at least one antiviral agent comprises at least one NNRTI.

38. The pharmaceutical composition as defined in claim 36, wherein the at least one antiviral agent comprises at least one NRTI.

39. The pharmaceutical composition as defined in claim 36, wherein the at least one antiviral agent comprises at least one protease inhibitor.

40. The pharmaceutical composition as defined in claim 36, wherein the at least one antiviral agent comprises at least one entry inhibitor.

41. The pharmaceutical composition as defined in claim 36, wherein the at least one antiviral agent comprises at least one integrase inhibitor.

42. Use of a pharmaceutical composition according to any one of claims 35 to 41 for the treatment of an HIV infection in a mammal having or at risk of having the infection.

43. A method of treating an HIV infection in a mammal having or at risk of having the infection, the method comprising administering to the mammal a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 34 or a pharmaceutically acceptable salt or ester

thereof, or a composition according to any one of claims 35 to 41.

44. A method of treating an HIV infection in a mammal having or at risk of having the infection, the method comprising administering to the mammal a therapeutically effective amount of a combination of a compound of formula (I) according to any one of claims 1 to 33 or a pharmaceutically acceptable salt or ester thereof, and at least one other antiviral agent; or a composition according to any one of claims 35 to 41.

45. Use of a compound of formula (I) according to any one of claims 1 to 33, or a pharmaceutically acceptable salt or ester thereof, for the treatment of an HIV infection in a mammal having or at risk of having the infection.

46. Use of a compound of formula (I) according to any one of claims 1 to 33, or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament for the treatment of an HIV infection in a mammal having or at risk of having the infection.

47. An article of manufacture comprising a composition effective to treat an HIV infection; and packaging material comprising a label which indicates that the composition can be used to treat infection by HIV; wherein the composition comprises a compound of formula (I) according to any one of claims 1 to 33 or a pharmaceutically acceptable salt or ester thereof.

48. A method of inhibiting the replication of HIV comprising exposing the virus to an effective amount of the compound of formula (I) according to any one of claims 1 to 33 or a salt or ester thereof, under conditions where replication of HIV is inhibited.

49. Use of a compounds of formula (I) according to any one of claims 1 to 33, to inhibit the activity of the HIV integrase enzyme.

50. Use of a compound of formula (I) according to any one of claims 1 to 33, or a salt or ester thereof, to inhibit the replication of HIV.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/001941

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 413/04*** (2006.01) , ***A61K 31/47*** (2006.01) , ***A61K 31/4709*** (2006.01) , ***A61K 31/538*** (2006.01) , ***A61P 31/18*** (2006.01) , ***C07D 215/02*** (2006.01) ***C07D 405/04*** (2006.01) , ***C07D 405/14*** (2006.01) , ***C07D 413/14*** (2006.01) , ***C07D 417/12*** (2006.01) , ***C07D 417/14*** (2006.01) , ***C07D 491/06*** (2006.01)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 413/04 , A61K 31/47, A61K 31/4709, A61K 31/538, A61P 31/18, C07D 215/02, C07D 405/04 , C07D 405/14 , C07D 413/14 , C07D 417/12 , C07D 417/14 , C07D 491/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

STN; Canadian Patent Database; Delphion; Espacenet; Google Patent; PubMed; Royal Society of Chemistry Publication Search; Google Scholar; Organic Chemistry Portal; J-Stage and ScienceDirect. Keywords: quinoline; HIV inhibitors; nonnucleoside reverse transcriptase inhibitors; quinoline acetic acid; quinoline carboxylic acid; Tsantrizos (name of inventor).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2007/131350 (TSANTRIZOS, YS et al.) 22 November 2007 Whole document	1-50
A	US6069151 (DYKE, HJ et al.) 30 May 2007 Whole document	1-50
A	US6670377 (MCKOUAR, K et al.) 30 December 2003 Whole document	1-50
A	CA2446324 (MUELLER, W et al.) 28 November 2002 Whole document	1-50
A	"Synthesis and Biological Activity of Quinolyl Acetic Acid Derivatives" *Journal of Pharmaceutical Sciences* **1973**, 2028-30 (KOHL, H et al.)	1-50
A	"Friedlander Syntheses with o-Aminoaryl Ketones. III. Acid-catalyzed Condensations of o-AMinobenzophenone with polyfunctional Carbonyl Compounds (1,2)" *Journal of Heterocyclic Chemistry* **1967**, 565-570 (FEHNEL, E)	1-50

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2009 (13-01-2009)	13 February 2009 (13-02-2009)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Wendy Young 819- 934-0477

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Styrylquinoline Derivatives: A New Class of Potent HIV-1 Integrase Inhibitors that Block HIV-1 Replication in CEM Cells." *J. Med. Chem.* **1998**, *41*, 2846-2857 (MEKOUAR, K et al.)	1-50
A	"Structure-Activity Relationships and Binding Mode of Styrylquinolines as Potent Inhibitors of HIV-I Integrase and Replication of HIV-1 in Cell Culture." *J. Med. Chem.* **2000**, *43*, 1533-1540 (ZOUBIRI, F et al.)	1-50

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/001941

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

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

1. [X] Claim Nos. : 43, 44 and 48

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 43, 44 and 48 are each directed to a method of medical treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. Regardless, this Authority has carried out a search based on the alleged effects or purposes, i.e. treatment of HIV infections by inhibiting HIV replication, of the present compounds of formula (I).

2. [ ] Claim Nos. :

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

3. [ ] Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2008/001941

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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		AU 711587B2	14-10-1999
		AU 735573B2	12-07-2001
		AU 4875897A	29-05-1998
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		WO 02094789A1	28-11-2002