

## **INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION**

### **RELATED APPLICATIONS**

This application claims benefit of U.S. Serial No. 60/988686, filed November 16, 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.

The inherent genetic variation within HIV has led to the identification of many HIV mutants, commonly referred to as variants, which exhibit altered drug susceptibility. On the integrase enzyme, residues 124 and 125 are recognized as highly variable across the HIV-1 virus from infected patients found in major market and developing countries. The approximate prevalence of these integrase variants are Thr124/Thr125 (44%), Ala124/Thr125 (17%), Ala124/Ala125 (16%), Thr124/Ala125 (10%), Asn124/Thr125 (6%), and Asn124/Ala125 (1%) for viruses sequenced from major market countries reported in the Los Alamos database

(<http://www.hiv.lanl.gov/content/hiv-db>). These integrase variants may be generated using known methods in the art and publicly available polypeptide sequences for the integrase enzyme, for example from the NL4.3 strain of HIV-1 integrase (SEQ ID NO: 1).

#### SUMMARY OF THE INVENTION

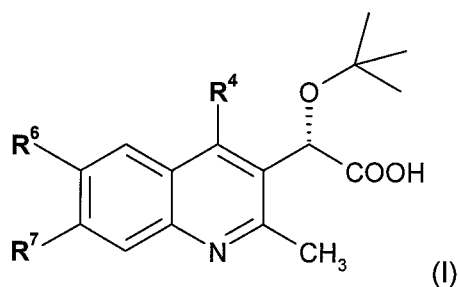
The present invention provides a novel series of compounds having inhibitory activity against HIV replication. The compounds of the present invention have an affinity for the HIV integrase enzyme. Therefore, the compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication. The compounds of the invention exhibit at least one of the following surprising advantages:

- unexpectedly good activity in a cell-based HIV-1 replication assay in four of the major integrase variants at residues 124/125 (Thr124/Thr125, Ala124/Thr125, Ala124/Ala125 and Thr124/Ala125); and/or
- unexpectedly good activity in a cell-based HIV-1 replication assay in all six of the major integrase variants at residues 124/125 (Thr124/Thr125, Ala124/Thr125, Ala124/Ala125, Thr124/Ala125, Asn124/Thr125, and Asn124/Ala125); and/or
- unexpectedly good pharmacological properties.

The compounds of the invention exhibit unexpectedly good potency against four of major integrase variants at the 124/125 residues (~> 85% natural abundance) and/or all six of the major integrase variants at the 124/125 residues. The implication of this unexpectedly good potency observed across the aforementioned 124/125 variable residues is that some HIV infected patients, who carry a virus with 124/125 variant residues of integrase and who have a pre-existing anti-viral resistance against drugs of this class, may be expected to respond to the compounds of the invention.

Further objects of this invention arise for the one skilled in the art from the following description and the examples.

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



wherein

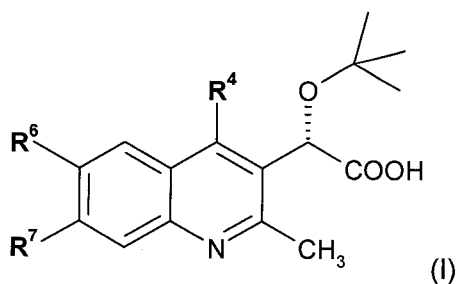
**R<sup>4</sup>** is aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>1-6</sub>)haloalkyl, (C<sub>3-7</sub>)cycloalkyl, -OH, -O(C<sub>1-6</sub>)alkyl, -SH, -S(C<sub>1-6</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>; wherein the (C<sub>1-6</sub>)alkyl is optionally substituted with hydroxy, cyano or oxo;

**R<sup>6</sup>** and **R<sup>7</sup>** are each independently selected from H, halo, (C<sub>1-6</sub>)alkyl and (C<sub>1-6</sub>)haloalkyl;

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;

or a salt or an ester thereof.

Another aspect of the invention provides an isomer, racemate, enantiomer or diastereomer of compounds of formula (I):



wherein

**R<sup>4</sup>** is aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>1-6</sub>)haloalkyl, (C<sub>3-7</sub>)cycloalkyl, -OH, -O(C<sub>1-6</sub>)alkyl, -SH, -S(C<sub>1-6</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>; wherein the (C<sub>1-6</sub>)alkyl is optionally substituted with hydroxy, cyano or oxo; and wherein the aryl is not

monosubstituted at the para position;

$R^6$  and  $R^7$  are each independently selected from H, halo,  $(C_{1-6})$ alkyl and  $(C_{1-6})$ haloalkyl;

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;  
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, exhibiting at least one of the following surprising advantages:

- unexpectedly good activity in a cell-based HIV-1 replication assay in four of the major integrase variants at residues 124/125 (Thr124/Thr125, Ala124/Thr125, Ala124/Ala125 and Thr124/Ala125); and/or
- unexpectedly good activity in a cell-based HIV-1 replication assay in all six of the major integrase variants at residues 124/125 (Thr124/Thr125, Ala124/Thr125, Ala124/Ala125, Thr124/Ala125, Asn124/Thr125, and Asn124/Ala125); and/or
- unexpectedly good pharmacological properties.

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 compound 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<sub>1-n</sub>)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<sub>1-6</sub>)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<sub>2-n</sub>)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<sub>2-n</sub>)alkenyl" is understood to encompass individual stereoisomers where possible, including but not limited to (*E*) and (*Z*) isomers, and mixtures thereof. When a (C<sub>2-n</sub>)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<sub>3-m</sub>)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 "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 "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 be 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 carbocycle may be substituted. When the carbocycle is substituted, it is understood that substituents may be attached to any carbon atom 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**" 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. 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 "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<sub>1-n</sub>)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<sub>1-n</sub>)haloalkyl include but are not limited to chloromethyl, chloroethyl, dichloroethyl, bromomethyl, bromoethyl, dibromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl and difluoroethyl.

The terms “-O-(C<sub>1-n</sub>)alkyl” or “(C<sub>1-n</sub>)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<sub>1-n</sub>)alkyl include but are not limited to methoxy (CH<sub>3</sub>O-), ethoxy (CH<sub>3</sub>CH<sub>2</sub>O-), propoxy (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>O-), 1-methylethoxy (*iso*-propoxy; (CH<sub>3</sub>)<sub>2</sub>CH-O-) and 1,1-dimethylethoxy (*tert*-butoxy; (CH<sub>3</sub>)<sub>3</sub>C-O-). When an -O-(C<sub>1-n</sub>)alkyl radical is substituted, it is understood to be substituted on the (C<sub>1-n</sub>)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 terms “-S-(C<sub>1-n</sub>)alkyl” or “(C<sub>1-n</sub>)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<sub>1-n</sub>)alkyl include but are not limited to methylthio (CH<sub>3</sub>S-), ethylthio (CH<sub>3</sub>CH<sub>2</sub>S-), propylthio (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>S-), 1-methylethylthio (*isopropyl*thio; (CH<sub>3</sub>)<sub>2</sub>CH-S-) and 1,1-dimethylethylthio (*tert*-butylthio; (CH<sub>3</sub>)<sub>3</sub>C-S-). When -S-(C<sub>1-n</sub>)alkyl radical, or an oxidized derivative thereof, such as an -SO-(C<sub>1-n</sub>)alkyl radical or an -SO<sub>2</sub>-(C<sub>1-n</sub>)alkyl radical, is substituted, each is understood to be substituted on the (C<sub>1-n</sub>)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 “cyano” as used herein is intended to mean an carbon atom attached to a nitrogen atom as a substituent by a triple bond.

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-phenamine, 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, heterocyclalkyl, 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<sub>1-4</sub>)alkyl or (C<sub>1-4</sub>)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<sub>1-16</sub>)alkyl ester, an unsubstituted benzyl ester or a benzyl ester substituted with at least one halogen, (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)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 detectable 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.

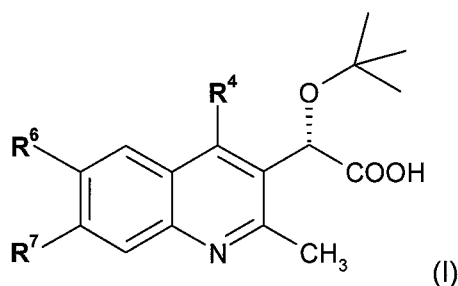
The term “inhibitor of HIV replication” as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro*, *ex vivo* or *in vivo*.

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):



according to this invention are described in detail.

**R<sup>4</sup>:**

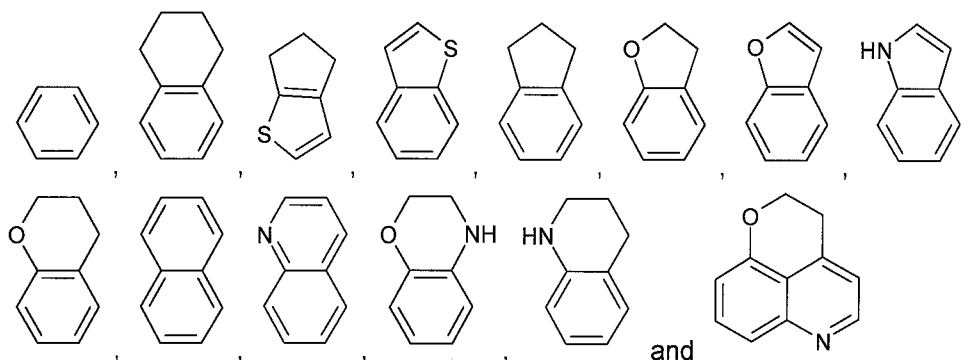
- R<sup>4</sup>-A:** In one embodiment, **R<sup>4</sup>** is aryl or **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>1-6</sub>)haloalkyl, (C<sub>3-7</sub>)cycloalkyl, -OH, -O(C<sub>1-6</sub>)alkyl, -SH, -S(C<sub>1-6</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>; wherein the (C<sub>1-6</sub>)alkyl is optionally substituted with hydroxy, cyano or oxo.
- R<sup>4</sup>-B:** In another embodiment, **R<sup>4</sup>** is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>1-6</sub>)haloalkyl, (C<sub>3-7</sub>)cycloalkyl, -OH, -O(C<sub>1-6</sub>)alkyl, -SH, -S(C<sub>1-6</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>.
- R<sup>4</sup>-C:** In another embodiment, **R<sup>4</sup>** is naphthyl or phenyl, optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)haloalkyl, -O(C<sub>1-4</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>.
- R<sup>4</sup>-D:** In another embodiment, **R<sup>4</sup>** is phenyl optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)haloalkyl, -O(C<sub>1-4</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>.
- R<sup>4</sup>-E:** In one embodiment, **R<sup>4</sup>** is **Het** optionally substituted with 1 to 2 substituents each independently selected from halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl.
- R<sup>4</sup>-F:** In one embodiment, **R<sup>4</sup>** is **Het** optionally substituted with 1 to 2 substituents each independently selected from Cl, F, CH<sub>3</sub> and CH<sub>2</sub>CH<sub>3</sub> wherein said **Het** is defined as a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 2 heteroatoms, each independently selected from O, N and S.
- R<sup>4</sup>-G:** In one embodiment, **R<sup>4</sup>** is **Het** optionally substituted with 1 to 2 substituents each independently selected from halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl, wherein said **Het** is defined as a 9- or 10-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 2 heteroatoms, each

independently selected from O, N and S.

**R<sup>4</sup>-H:** In another embodiment, **R<sup>4</sup>** is phenyl optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)haloalkyl, -O(C<sub>1-4</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub> or **R<sup>4</sup>** is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-4</sub>)alkyl and O-(C<sub>1-4</sub>)alkyl, wherein said **Het** is defined as a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 2 heteroatoms, each independently selected from O, N and S.

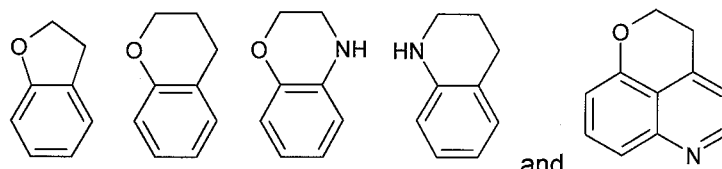
**R<sup>4</sup>-I:** In another embodiment, **R<sup>4</sup>** is phenyl optionally substituted with 1 to 3 substituents each independently selected from F, Cl, Br, -CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>F, -CH<sub>2</sub>CH<sub>2</sub>F, -OCH<sub>3</sub> and -NH<sub>2</sub> or **R<sup>4</sup>** is **Het** optionally substituted with 1 to 3 substituents each independently selected from Cl, F, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub> and OCH<sub>3</sub>, wherein said **Het** is defined as a 7- or 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 3 heteroatoms, each independently selected from O, N and S.

**R<sup>4</sup>-J:** In another embodiment, **R<sup>4</sup>** is selected from:



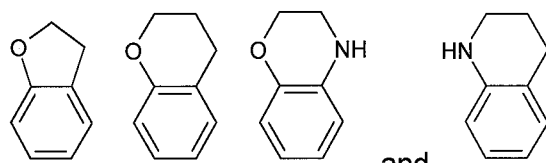
being optionally substituted 1 to 3 times with halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl.

**R<sup>4</sup>-K:** In another embodiment, **R<sup>4</sup>** is selected from:



being optionally substituted 1 to 2 times with halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl.

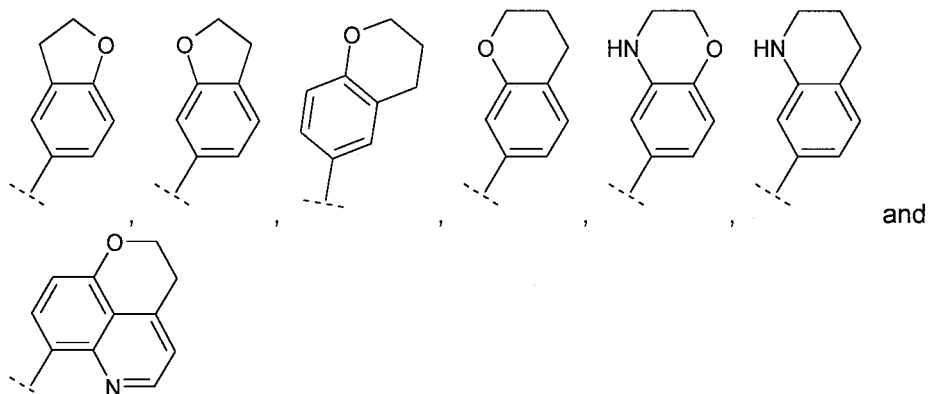
**R<sup>4</sup>-L:** In another embodiment, **R<sup>4</sup>** is selected from:



and

being optionally substituted 1 to 2 times with halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl.

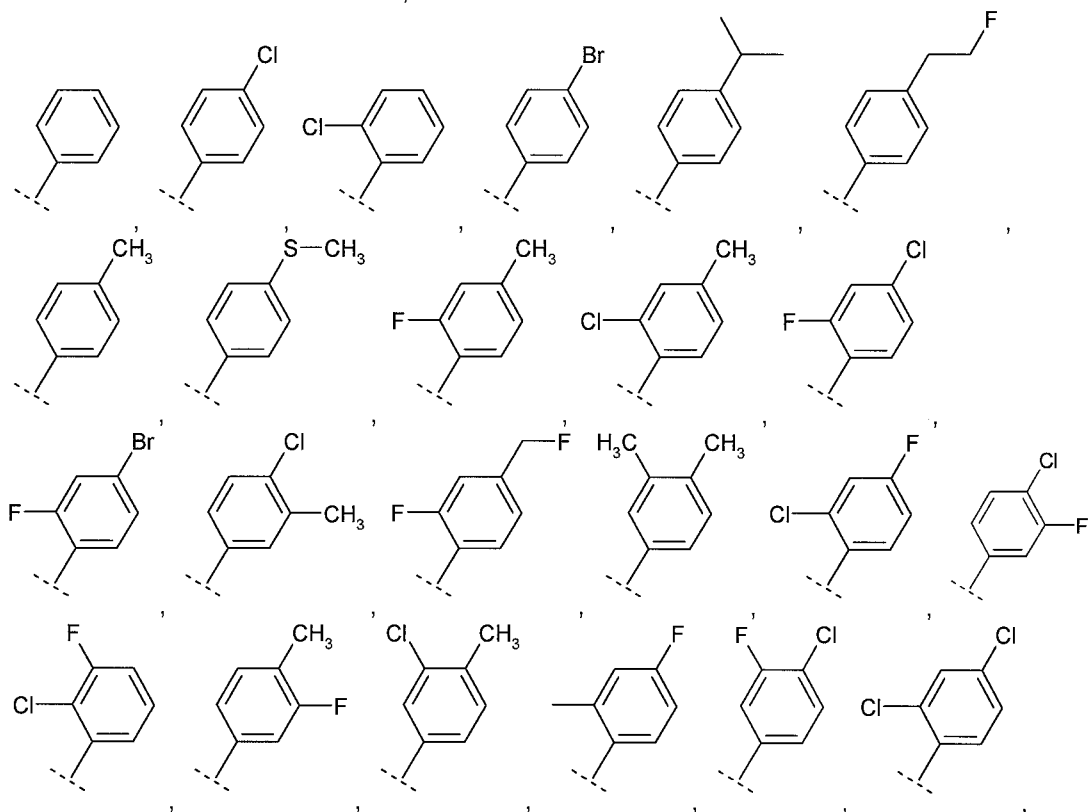
**R<sup>4</sup>-M:** In another embodiment, **R<sup>4</sup>** is selected from:

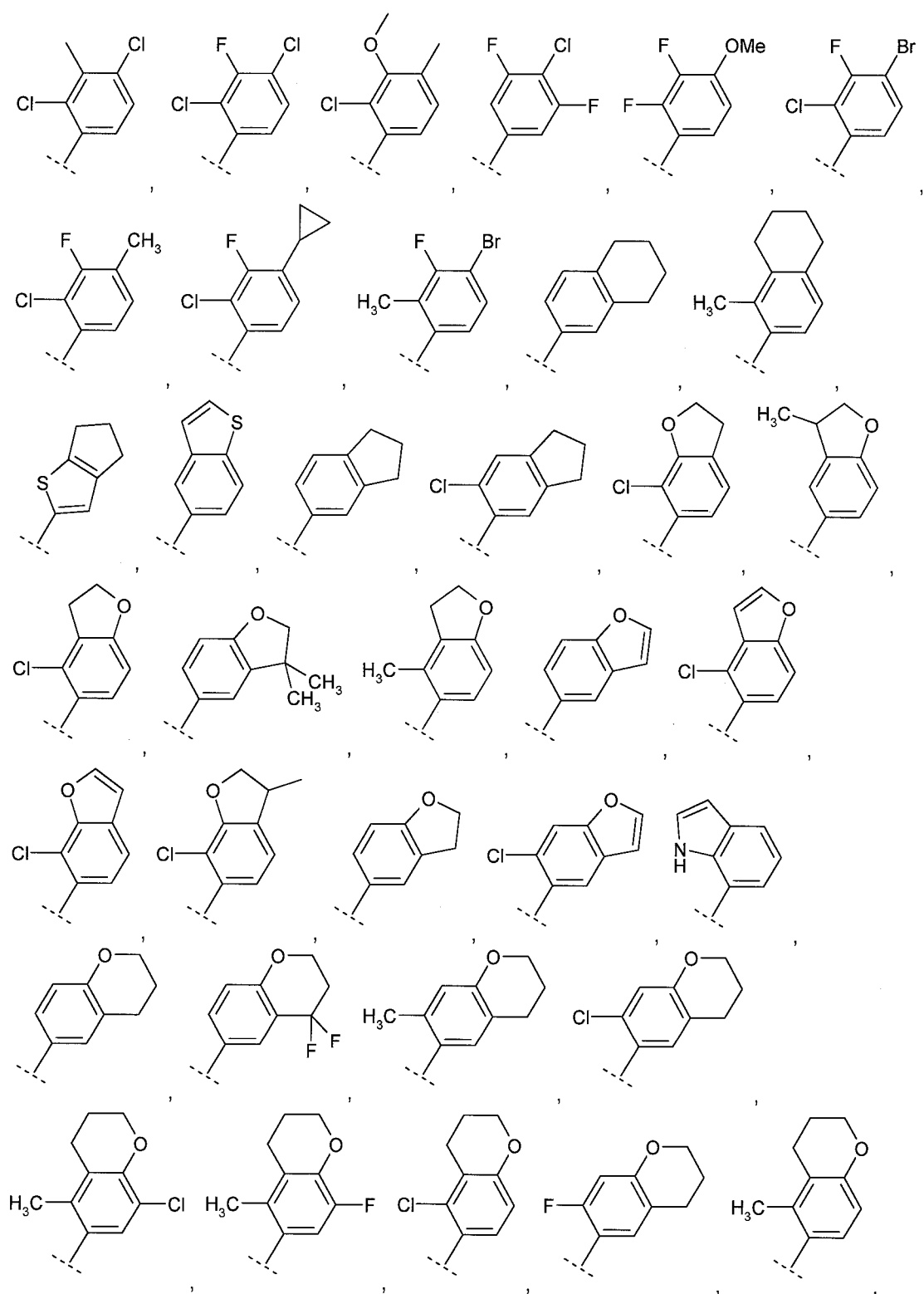


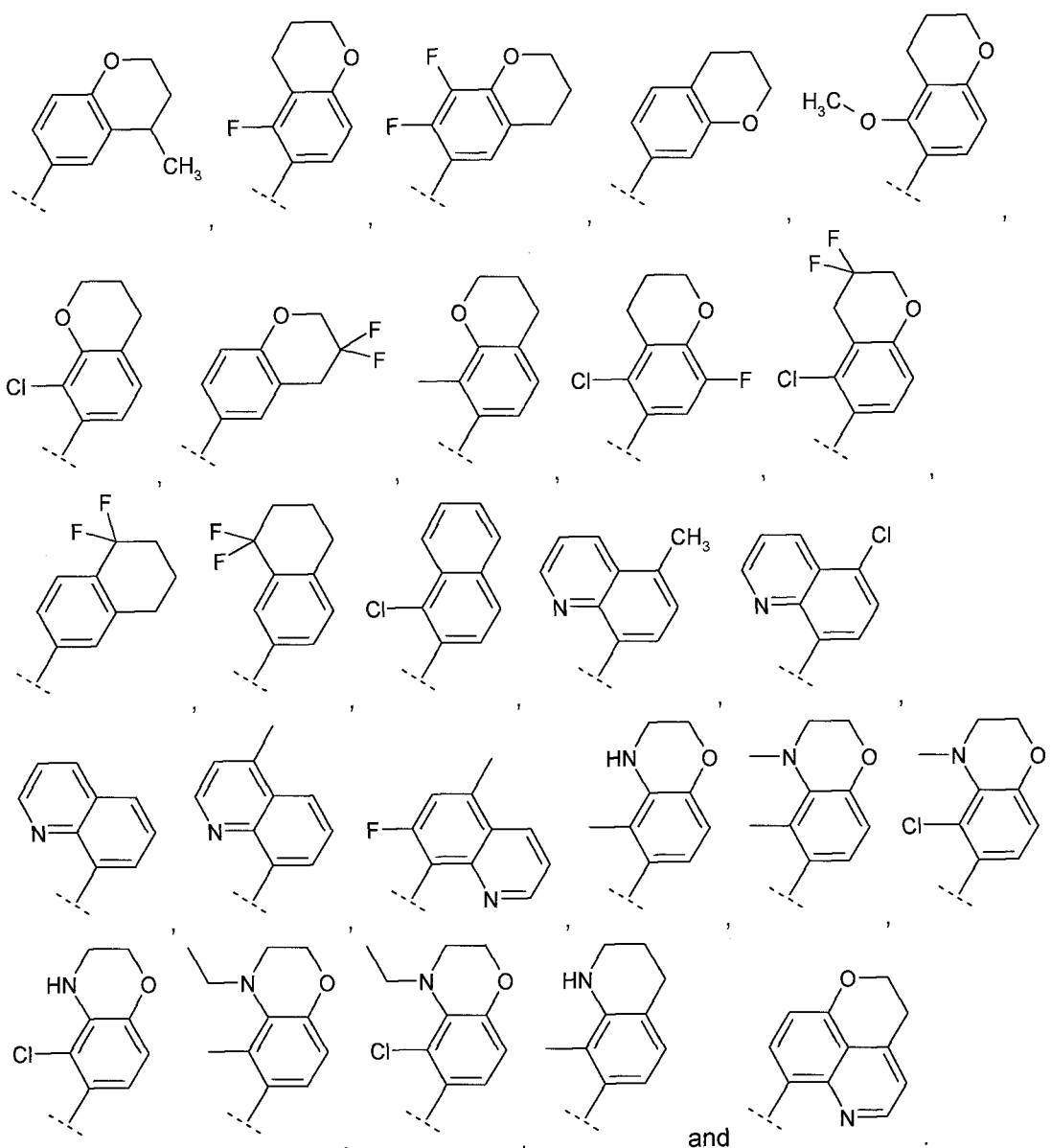
and

being optionally substituted 1 to 2 times with halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl.

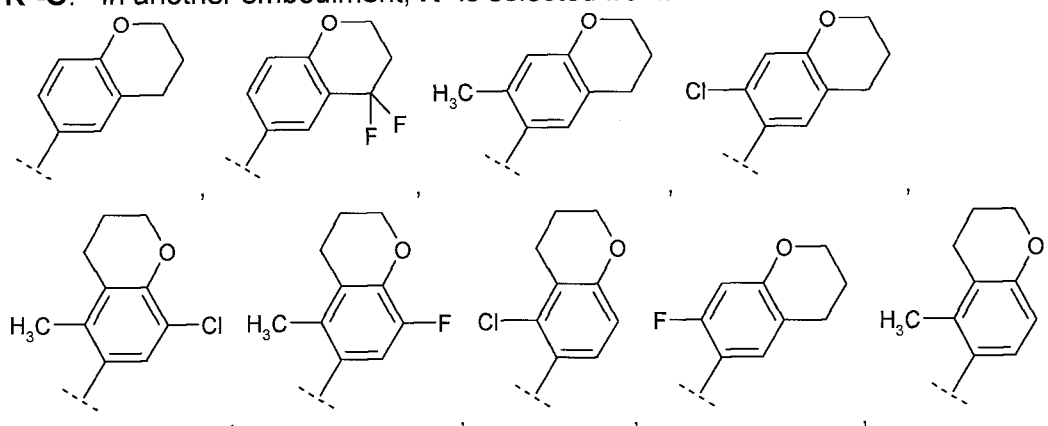
**R<sup>4</sup>-N:** In another embodiment, **R<sup>4</sup>** is selected from:

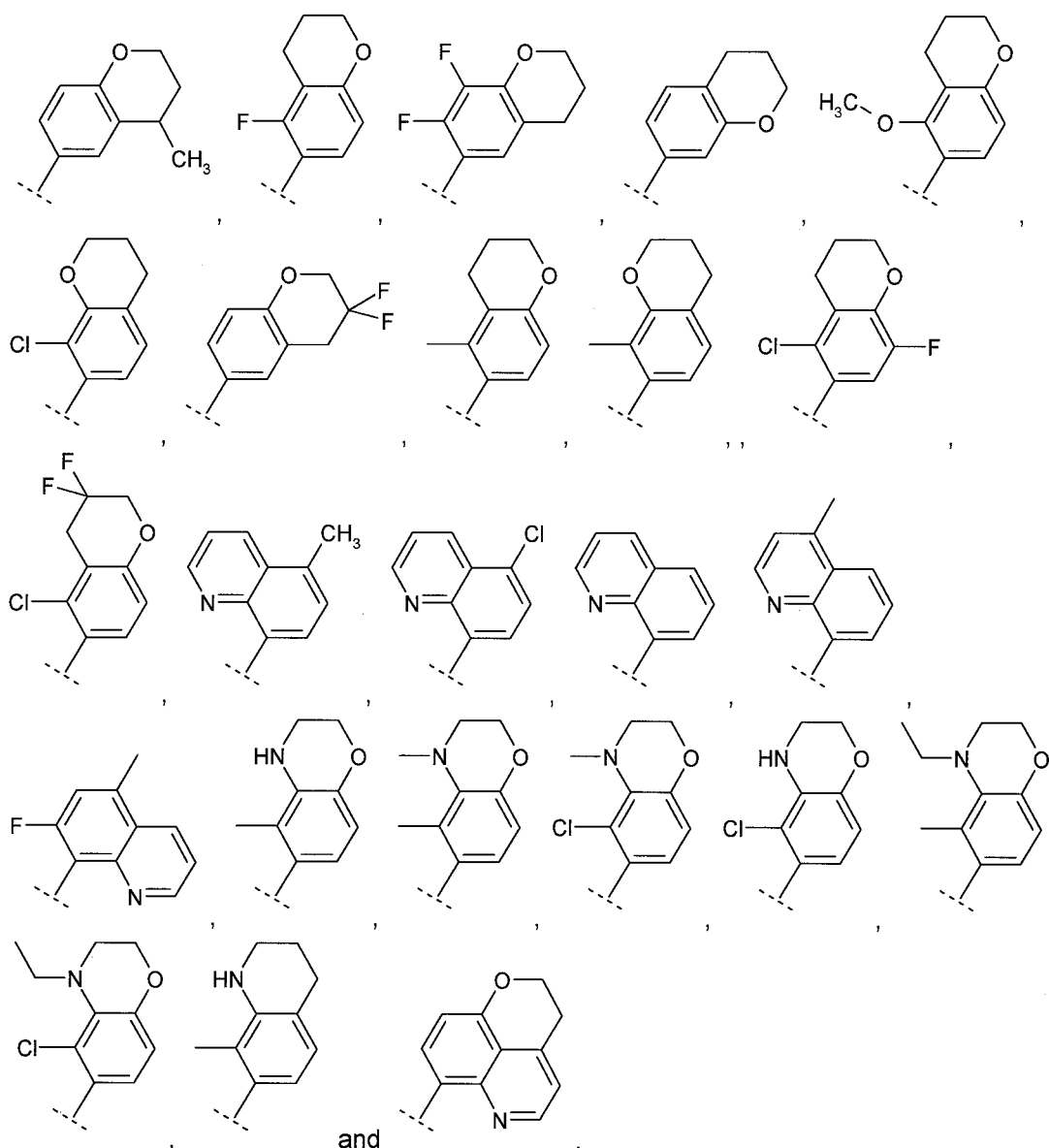






**R<sup>4</sup>-O:** In another embodiment, R<sup>4</sup> is selected from:

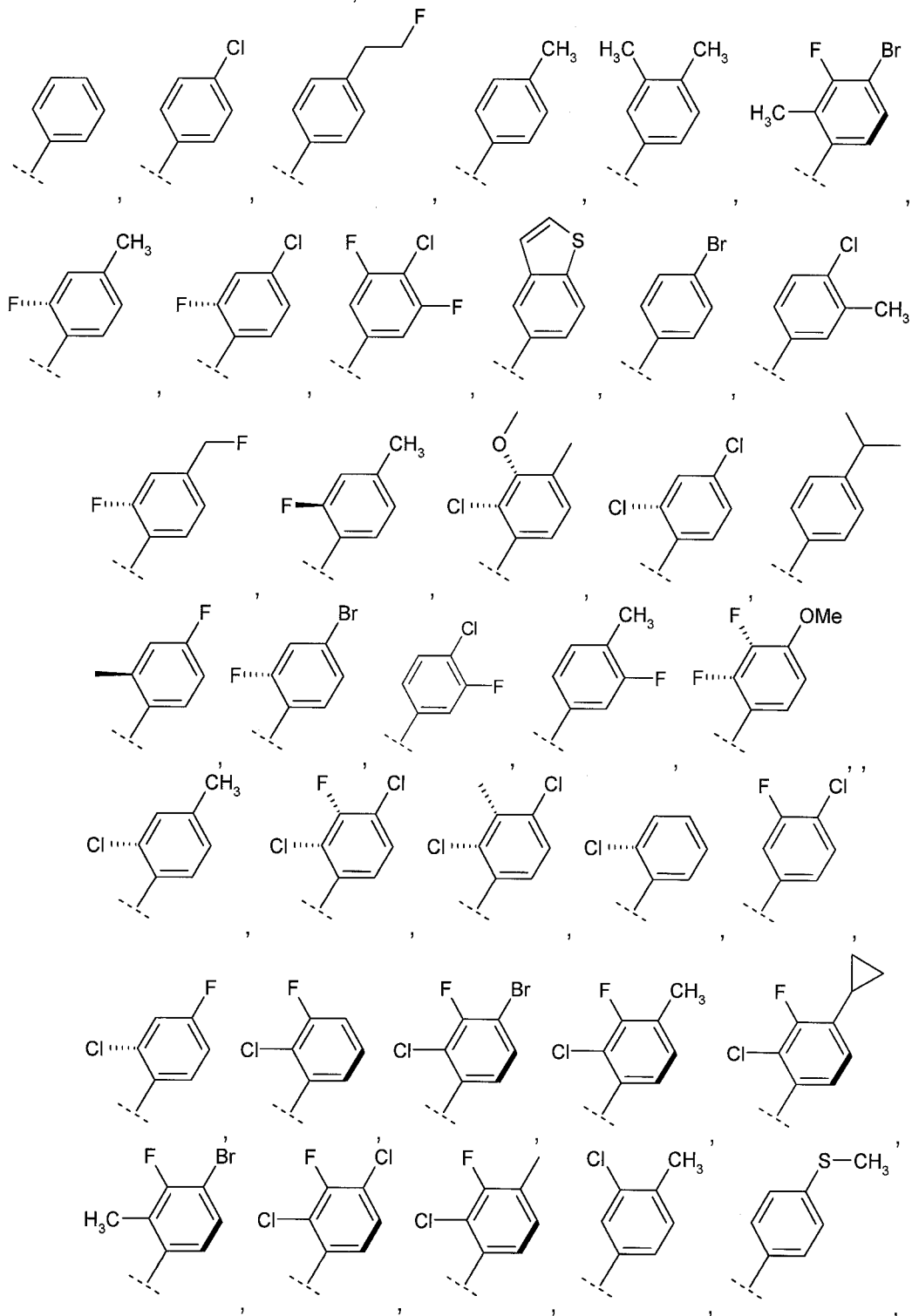


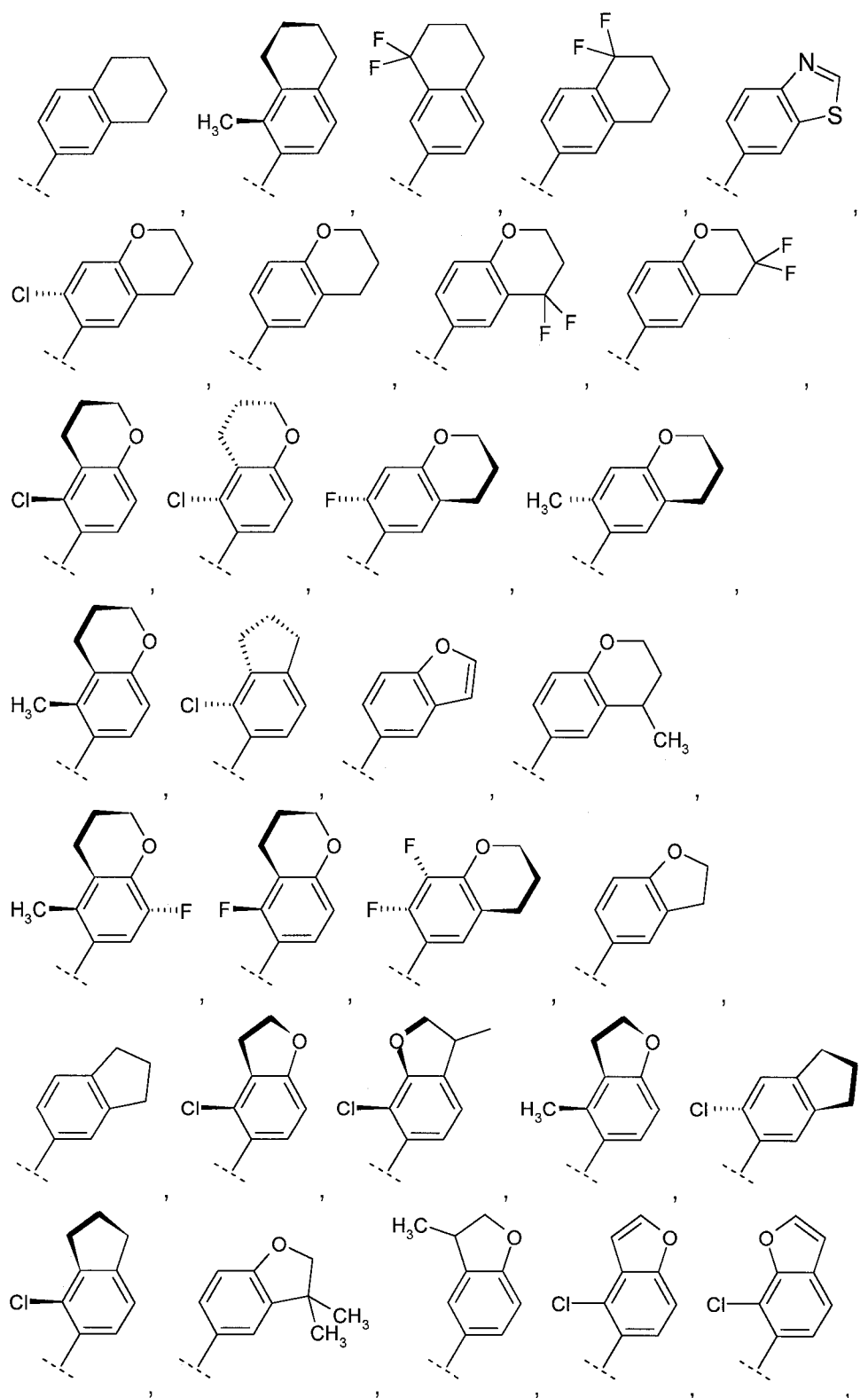


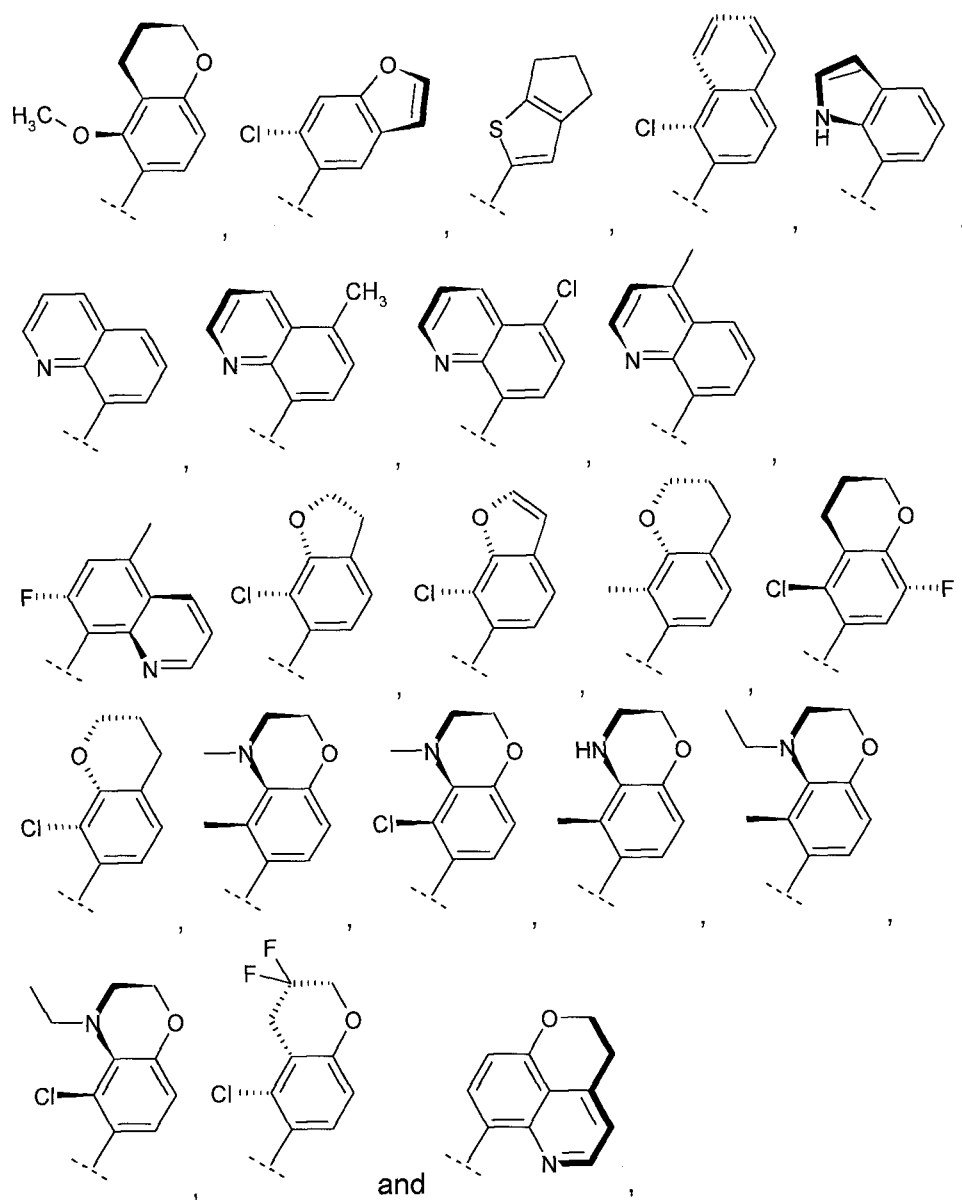
One skilled in the art will recognize that when the  $R^4$  substituent is not symmetrically substituted about the axis of rotation of the bond attaching  $R^4$  to **Core**, rotational isomers or atropisomers are possible. Compounds of the invention in which the  $R^4$  substituent is not symmetrically 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.

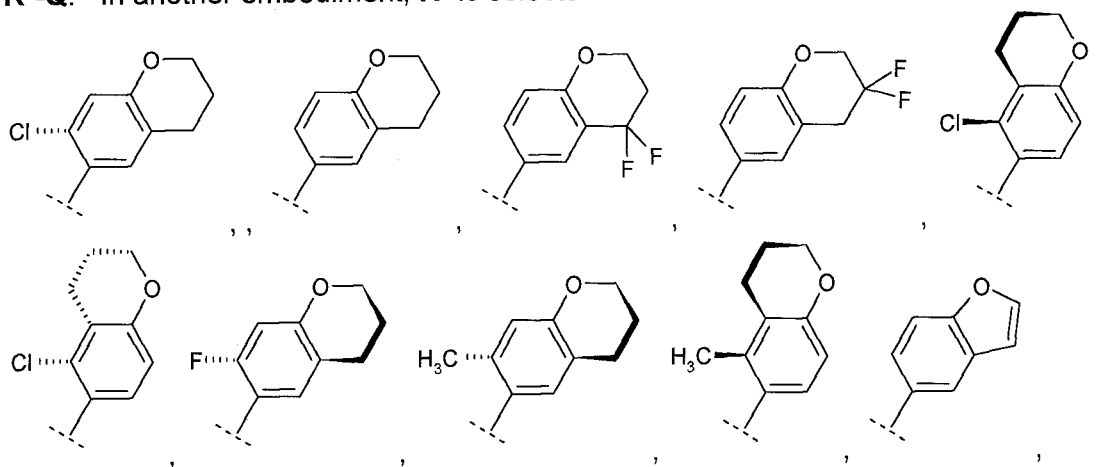
**R<sup>4</sup>-P:** In another embodiment, **R<sup>4</sup>** is selected from:

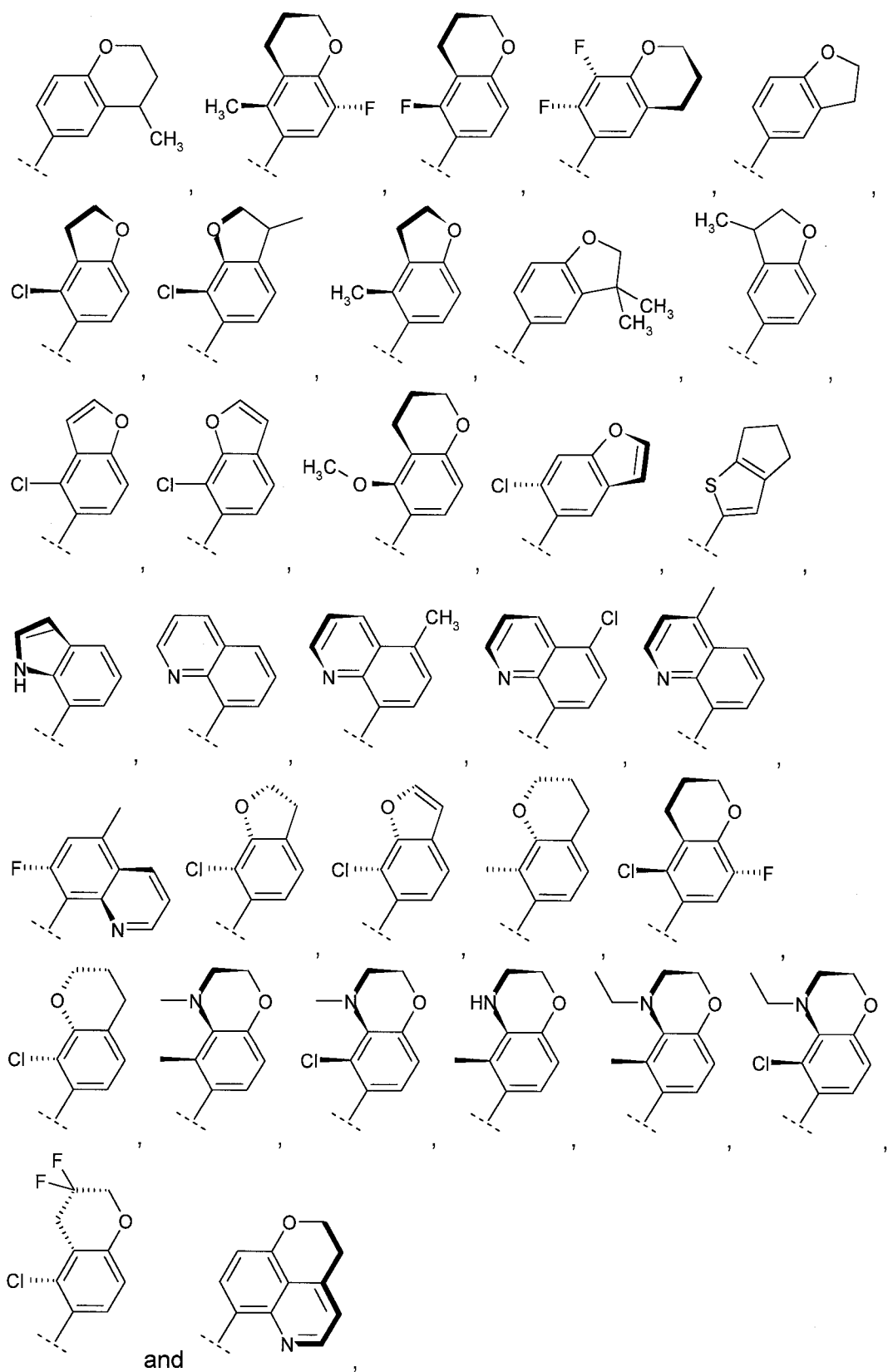






**R<sup>4</sup>-Q:** In another embodiment, **R<sup>4</sup>** is selected from:





**R<sup>4</sup>-R:** In another embodiment, **R<sup>4</sup>** is aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected

from halo, (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>1-6</sub>)haloalkyl, (C<sub>3-7</sub>)cycloalkyl, -OH, -O(C<sub>1-6</sub>)alkyl, -SH, -S(C<sub>1-6</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>; wherein the (C<sub>1-6</sub>)alkyl is optionally substituted with hydroxy, cyano or oxo; and wherein the aryl is not monosubstituted at the para position;

Any and each individual definition of **R<sup>4</sup>** as set out herein may be combined with any and each individual definition of **R<sup>6</sup>** and **R<sup>7</sup>** as set out herein.

**R<sup>6</sup>:**

**R<sup>6</sup>-A:** In one embodiment, **R<sup>6</sup>** is H, halo, (C<sub>1-6</sub>)alkyl or (C<sub>1-6</sub>)haloalkyl.

**R<sup>6</sup>-B:** In another embodiment, **R<sup>6</sup>** is H, halo or (C<sub>1-3</sub>)alkyl.

**R<sup>6</sup>-C:** In another embodiment, **R<sup>6</sup>** is H, F, Cl or (C<sub>1-2</sub>)alkyl.

**R<sup>6</sup>-D:** In another embodiment, **R<sup>6</sup>** is H, F, Cl or CH<sub>3</sub>.

**R<sup>6</sup>-E:** In another embodiment, **R<sup>6</sup>** is H, CH<sub>3</sub> or CH<sub>2</sub>CH<sub>3</sub>.

**R<sup>6</sup>-F:** In another embodiment, **R<sup>6</sup>** is H or CH<sub>3</sub>.

**R<sup>6</sup>-G:** In another embodiment, **R<sup>6</sup>** is H.

Any and each individual definition of **R<sup>6</sup>** as set out herein may be combined with any and each individual definition of **R<sup>4</sup>** and **R<sup>7</sup>** as set out herein.

**R<sup>7</sup>:**

**R<sup>7</sup>-A:** In one embodiment, **R<sup>7</sup>** is H, halo, (C<sub>1-6</sub>)alkyl or (C<sub>1-6</sub>)haloalkyl.

**R<sup>7</sup>-B:** In another embodiment, **R<sup>7</sup>** is H, halo or (C<sub>1-3</sub>)alkyl.

**R<sup>7</sup>-C:** In another embodiment, **R<sup>7</sup>** is H, F, Cl or (C<sub>1-2</sub>)alkyl.

**R<sup>7</sup>-D:** In another embodiment, **R<sup>7</sup>** is H, F, Cl or CH<sub>3</sub>.

**R<sup>7</sup>-E:** In one embodiment, **R<sup>7</sup>** is H, F or CH<sub>3</sub>.

**R<sup>7</sup>-F:** In one embodiment, **R<sup>7</sup>** is H or CH<sub>3</sub>.

**R<sup>7</sup>-G:** In another embodiment, **R<sup>7</sup>** is H.

Any and each individual definition of **R<sup>7</sup>** as set out herein may be combined with any and each individual definition of **R<sup>4</sup>** and **R<sup>6</sup>** 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 | R <sup>4</sup>    | R <sup>6</sup>    | R <sup>7</sup>    |
|------------|-------------------|-------------------|-------------------|
| E-1        | R <sup>4</sup> -A | R <sup>6</sup> -B | R <sup>7</sup> -C |
| E-2        | R <sup>4</sup> -A | R <sup>6</sup> -D | R <sup>7</sup> -C |
| E-3        | R <sup>4</sup> -A | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-4        | R <sup>4</sup> -A | R <sup>6</sup> -F | R <sup>7</sup> -A |
| E-5        | R <sup>4</sup> -A | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-6        | R <sup>4</sup> -B | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-7        | R <sup>4</sup> -B | R <sup>6</sup> -B | R <sup>7</sup> -F |
| E-8        | R <sup>4</sup> -B | R <sup>6</sup> -F | R <sup>7</sup> -A |
| E-9        | R <sup>4</sup> -C | R <sup>6</sup> -A | R <sup>7</sup> -A |
| E-10       | R <sup>4</sup> -C | R <sup>6</sup> -D | R <sup>7</sup> -A |
| E-11       | R <sup>4</sup> -C | R <sup>6</sup> -F | R <sup>7</sup> -D |
| E-12       | R <sup>4</sup> -D | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-13       | R <sup>4</sup> -D | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-14       | R <sup>4</sup> -D | R <sup>6</sup> -G | R <sup>7</sup> -F |
| E-15       | R <sup>4</sup> -D | R <sup>6</sup> -E | R <sup>7</sup> -G |
| E-16       | R <sup>4</sup> -D | R <sup>6</sup> -D | R <sup>7</sup> -C |
| E-17       | R <sup>4</sup> -D | R <sup>6</sup> -E | R <sup>7</sup> -C |
| E-18       | R <sup>4</sup> -E | R <sup>6</sup> -C | R <sup>7</sup> -A |
| E-19       | R <sup>4</sup> -E | R <sup>6</sup> -B | R <sup>7</sup> -C |
| E-20       | R <sup>4</sup> -E | R <sup>6</sup> -B | R <sup>7</sup> -B |
| E-21       | R <sup>4</sup> -E | R <sup>6</sup> -B | R <sup>7</sup> -E |
| E-22       | R <sup>4</sup> -E | R <sup>6</sup> -E | R <sup>7</sup> -C |
| E-23       | R <sup>4</sup> -F | R <sup>6</sup> -D | R <sup>7</sup> -A |
| E-24       | R <sup>4</sup> -F | R <sup>6</sup> -E | R <sup>7</sup> -C |
| E-25       | R <sup>4</sup> -F | R <sup>6</sup> -C | R <sup>7</sup> -B |
| E-26       | R <sup>4</sup> -F | R <sup>6</sup> -B | R <sup>7</sup> -E |
| E-27       | R <sup>4</sup> -G | R <sup>6</sup> -A | R <sup>7</sup> -D |
| E-28       | R <sup>4</sup> -G | R <sup>6</sup> -C | R <sup>7</sup> -B |
| E-29       | R <sup>4</sup> -G | R <sup>6</sup> -B | R <sup>7</sup> -A |
| E-30       | R <sup>4</sup> -G | R <sup>6</sup> -B | R <sup>7</sup> -G |
| E-31       | R <sup>4</sup> -G | R <sup>6</sup> -A | R <sup>7</sup> -F |

| Embodiment | R <sup>4</sup>    | R <sup>6</sup>    | R <sup>7</sup>    |
|------------|-------------------|-------------------|-------------------|
| E-32       | R <sup>4</sup> -G | R <sup>6</sup> -A | R <sup>7</sup> -E |
| E-33       | R <sup>4</sup> -G | R <sup>6</sup> -C | R <sup>7</sup> -D |
| E-34       | R <sup>4</sup> -H | R <sup>6</sup> -C | R <sup>7</sup> -E |
| E-35       | R <sup>4</sup> -H | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-36       | R <sup>4</sup> -H | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-37       | R <sup>4</sup> -H | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-38       | R <sup>4</sup> -H | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-39       | R <sup>4</sup> -H | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-40       | R <sup>4</sup> -H | R <sup>6</sup> -G | R <sup>7</sup> -B |
| E-41       | R <sup>4</sup> -H | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-42       | R <sup>4</sup> -H | R <sup>6</sup> -F | R <sup>7</sup> -C |
| E-43       | R <sup>4</sup> -H | R <sup>6</sup> -G | R <sup>7</sup> -E |
| E-44       | R <sup>4</sup> -H | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-45       | R <sup>4</sup> -H | R <sup>6</sup> -D | R <sup>7</sup> -A |
| E-46       | R <sup>4</sup> -H | R <sup>6</sup> -A | R <sup>7</sup> -B |
| E-47       | R <sup>4</sup> -I | R <sup>6</sup> -C | R <sup>7</sup> -E |
| E-48       | R <sup>4</sup> -I | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-49       | R <sup>4</sup> -I | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-50       | R <sup>4</sup> -I | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-51       | R <sup>4</sup> -I | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-52       | R <sup>4</sup> -I | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-53       | R <sup>4</sup> -I | R <sup>6</sup> -B | R <sup>7</sup> -C |
| E-54       | R <sup>4</sup> -I | R <sup>6</sup> -A | R <sup>7</sup> -G |
| E-55       | R <sup>4</sup> -I | R <sup>6</sup> -B | R <sup>7</sup> -C |
| E-56       | R <sup>4</sup> -J | R <sup>6</sup> -C | R <sup>7</sup> -E |
| E-57       | R <sup>4</sup> -J | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-58       | R <sup>4</sup> -J | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-59       | R <sup>4</sup> -J | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-60       | R <sup>4</sup> -J | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-61       | R <sup>4</sup> -J | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-62       | R <sup>4</sup> -J | R <sup>6</sup> -F | R <sup>7</sup> -D |
| E-63       | R <sup>4</sup> -J | R <sup>6</sup> -A | R <sup>7</sup> -A |

| Embodiment | R <sup>4</sup>    | R <sup>6</sup>    | R <sup>7</sup>    |
|------------|-------------------|-------------------|-------------------|
| E-64       | R <sup>4</sup> -J | R <sup>6</sup> -F | R <sup>7</sup> -G |
| E-65       | R <sup>4</sup> -J | R <sup>6</sup> -G | R <sup>7</sup> -F |
| E-66       | R <sup>4</sup> -J | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-67       | R <sup>4</sup> -J | R <sup>6</sup> -D | R <sup>7</sup> -G |
| E-68       | R <sup>4</sup> -J | R <sup>6</sup> -G | R <sup>7</sup> -E |
| E-69       | R <sup>4</sup> -K | R <sup>6</sup> -C | R <sup>7</sup> -E |
| E-70       | R <sup>4</sup> -K | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-71       | R <sup>4</sup> -K | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-72       | R <sup>4</sup> -K | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-73       | R <sup>4</sup> -K | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-74       | R <sup>4</sup> -K | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-75       | R <sup>4</sup> -K | R <sup>6</sup> -G | R <sup>7</sup> -A |
| E-76       | R <sup>4</sup> -K | R <sup>6</sup> -B | R <sup>7</sup> -C |
| E-77       | R <sup>4</sup> -K | R <sup>6</sup> -G | R <sup>7</sup> -E |
| E-78       | R <sup>4</sup> -L | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-79       | R <sup>4</sup> -L | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-80       | R <sup>4</sup> -L | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-81       | R <sup>4</sup> -L | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-82       | R <sup>4</sup> -L | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-83       | R <sup>4</sup> -L | R <sup>6</sup> -G | R <sup>7</sup> -A |
| E-84       | R <sup>4</sup> -L | R <sup>6</sup> -B | R <sup>7</sup> -C |
| E-85       | R <sup>4</sup> -L | R <sup>6</sup> -G | R <sup>7</sup> -E |
| E-86       | R <sup>4</sup> -L | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-87       | R <sup>4</sup> -L | R <sup>6</sup> -F | R <sup>7</sup> -F |
| E-88       | R <sup>4</sup> -L | R <sup>6</sup> -F | R <sup>7</sup> -G |
| E-89       | R <sup>4</sup> -L | R <sup>6</sup> -A | R <sup>7</sup> -C |
| E-90       | R <sup>4</sup> -L | R <sup>6</sup> -D | R <sup>7</sup> -A |
| E-91       | R <sup>4</sup> -M | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-92       | R <sup>4</sup> -M | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-93       | R <sup>4</sup> -M | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-94       | R <sup>4</sup> -M | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-95       | R <sup>4</sup> -M | R <sup>6</sup> -E | R <sup>7</sup> -F |

| Embodiment | R <sup>4</sup>    | R <sup>6</sup>    | R <sup>7</sup>    |
|------------|-------------------|-------------------|-------------------|
| E-96       | R <sup>4</sup> -M | R <sup>6</sup> -G | R <sup>7</sup> -A |
| E-97       | R <sup>4</sup> -M | R <sup>6</sup> -B | R <sup>7</sup> -C |
| E-98       | R <sup>4</sup> -M | R <sup>6</sup> -G | R <sup>7</sup> -E |
| E-99       | R <sup>4</sup> -M | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-100      | R <sup>4</sup> -M | R <sup>6</sup> -F | R <sup>7</sup> -F |
| E-101      | R <sup>4</sup> -M | R <sup>6</sup> -F | R <sup>7</sup> -G |
| E-102      | R <sup>4</sup> -M | R <sup>6</sup> -A | R <sup>7</sup> -D |
| E-103      | R <sup>4</sup> -M | R <sup>6</sup> -C | R <sup>7</sup> -B |
| E-104      | R <sup>4</sup> -N | R <sup>6</sup> -C | R <sup>7</sup> -E |
| E-105      | R <sup>4</sup> -N | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-106      | R <sup>4</sup> -N | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-107      | R <sup>4</sup> -N | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-108      | R <sup>4</sup> -N | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-109      | R <sup>4</sup> -N | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-110      | R <sup>4</sup> -N | R <sup>6</sup> -F | R <sup>7</sup> -G |
| E-111      | R <sup>4</sup> -N | R <sup>6</sup> -B | R <sup>7</sup> -B |
| E-112      | R <sup>4</sup> -N | R <sup>6</sup> -G | R <sup>7</sup> -A |
| E-113      | R <sup>4</sup> -N | R <sup>6</sup> -A | R <sup>7</sup> -G |
| E-114      | R <sup>4</sup> -O | R <sup>6</sup> -C | R <sup>7</sup> -E |
| E-115      | R <sup>4</sup> -O | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-116      | R <sup>4</sup> -O | R <sup>6</sup> -D | R <sup>7</sup> -E |
| E-117      | R <sup>4</sup> -O | R <sup>6</sup> -D | R <sup>7</sup> -F |
| E-118      | R <sup>4</sup> -O | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-119      | R <sup>4</sup> -O | R <sup>6</sup> -E | R <sup>7</sup> -F |
| E-120      | R <sup>4</sup> -O | R <sup>6</sup> -B | R <sup>7</sup> -F |
| E-121      | R <sup>4</sup> -O | R <sup>6</sup> -G | R <sup>7</sup> -B |
| E-122      | R <sup>4</sup> -O | R <sup>6</sup> -F | R <sup>7</sup> -A |
| E-123      | R <sup>4</sup> -P | R <sup>6</sup> -B | R <sup>7</sup> -A |
| E-124      | R <sup>4</sup> -P | R <sup>6</sup> -C | R <sup>7</sup> -B |
| E-125      | R <sup>4</sup> -P | R <sup>6</sup> -D | R <sup>7</sup> -C |
| E-126      | R <sup>4</sup> -P | R <sup>6</sup> -E | R <sup>7</sup> -D |
| E-127      | R <sup>4</sup> -P | R <sup>6</sup> -F | R <sup>7</sup> -E |

| Embodiment | R <sup>4</sup>    | R <sup>6</sup>    | R <sup>7</sup>    |
|------------|-------------------|-------------------|-------------------|
| E-128      | R <sup>4</sup> -P | R <sup>6</sup> -G | R <sup>7</sup> -F |
| E-129      | R <sup>4</sup> -P | R <sup>6</sup> -A | R <sup>7</sup> -G |
| E-130      | R <sup>4</sup> -P | R <sup>6</sup> -A | R <sup>7</sup> -A |
| E-131      | R <sup>4</sup> -P | R <sup>6</sup> -B | R <sup>7</sup> -E |
| E-132      | R <sup>4</sup> -P | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-133      | R <sup>4</sup> -P | R <sup>6</sup> -D | R <sup>7</sup> -G |
| E-134      | R <sup>4</sup> -P | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-135      | R <sup>4</sup> -P | R <sup>6</sup> -F | R <sup>7</sup> -F |
| E-136      | R <sup>4</sup> -P | R <sup>6</sup> -G | R <sup>7</sup> -G |
| E-137      | R <sup>4</sup> -Q | R <sup>6</sup> -B | R <sup>7</sup> -A |
| E-138      | R <sup>4</sup> -Q | R <sup>6</sup> -C | R <sup>7</sup> -B |
| E-139      | R <sup>4</sup> -Q | R <sup>6</sup> -D | R <sup>7</sup> -C |
| E-140      | R <sup>4</sup> -Q | R <sup>6</sup> -E | R <sup>7</sup> -D |
| E-141      | R <sup>4</sup> -Q | R <sup>6</sup> -F | R <sup>7</sup> -E |
| E-142      | R <sup>4</sup> -Q | R <sup>6</sup> -G | R <sup>7</sup> -F |
| E-143      | R <sup>4</sup> -Q | R <sup>6</sup> -A | R <sup>7</sup> -G |
| E-144      | R <sup>4</sup> -Q | R <sup>6</sup> -A | R <sup>7</sup> -A |
| E-145      | R <sup>4</sup> -Q | R <sup>6</sup> -B | R <sup>7</sup> -E |
| E-146      | R <sup>4</sup> -Q | R <sup>6</sup> -C | R <sup>7</sup> -F |
| E-147      | R <sup>4</sup> -Q | R <sup>6</sup> -D | R <sup>7</sup> -G |
| E-148      | R <sup>4</sup> -Q | R <sup>6</sup> -E | R <sup>7</sup> -E |
| E-149      | R <sup>4</sup> -Q | R <sup>6</sup> -F | R <sup>7</sup> -F |
| E-150      | R <sup>4</sup> -Q | R <sup>6</sup> -G | R <sup>7</sup> -G |

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

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, powders, syrups, elixirs 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, diluents, 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. Popovich 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 moieties 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 displacement 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),  $\beta$ -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  $^{14}\text{C}$ ,  $^3\text{H}$ ,  $^{31}\text{P}$ ,  $^{121}\text{I}$ ,  $^{125}\text{I}$  and the like.

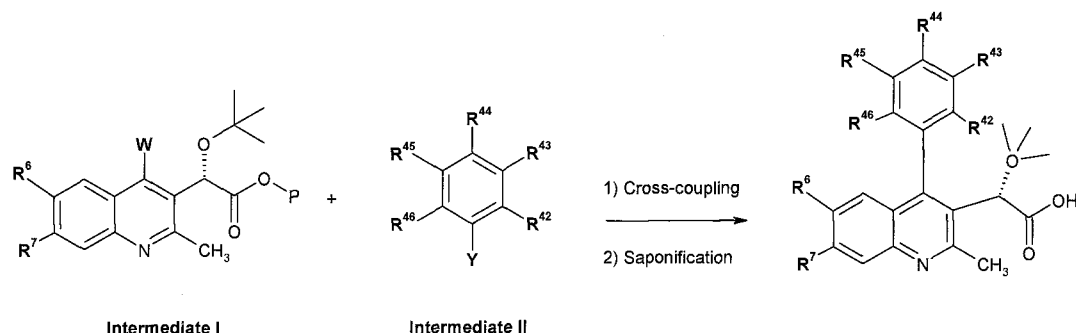
An affinity tag is a label which has a strong affinity for another moiety, designated herein as a binding partner. Such an affinity tag can be used to form a complex with the binding partner so that the complex may be selectively detected or separated from a mixture. Affinity tags include but are not 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<sup>®</sup> 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  $\text{R}^4$ ,  $\text{R}^6$  and  $\text{R}^7$  are as defined herein. Further instruction is provided to one skilled in the art by the specific examples set out herein below.

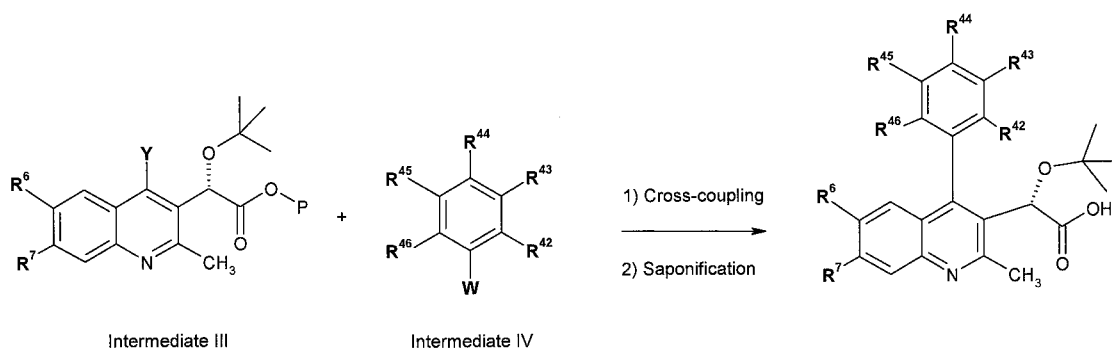
## Scheme 1: Assembly of inhibitors



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 intermediate II and the bromo or iodo derivative of I as shown above can lead, after saponification, to the compounds of formula (I).

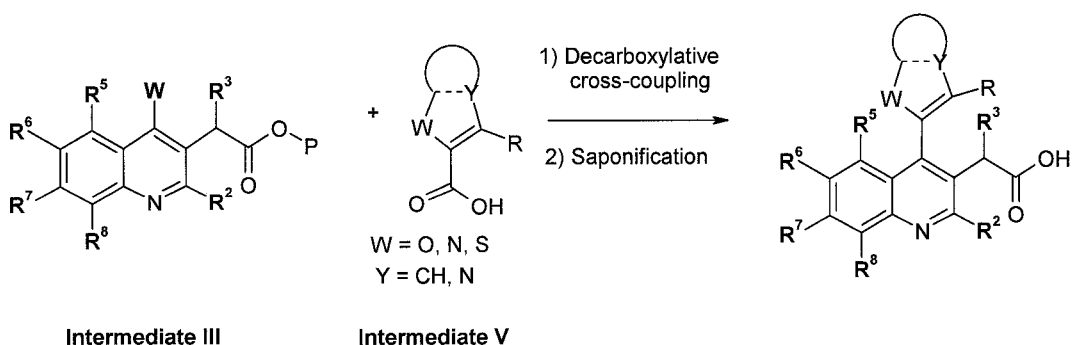
Alternatively, the same cross-coupling methods can be used by interchanging the coupling partners as shown below. For examples, Suzuki, Negishi, and Stille type cross-coupling between boronic acid or boronate ester derivative, the arylzinc reagent or the arylltin reagent of quinoline intermediate III 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).



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:

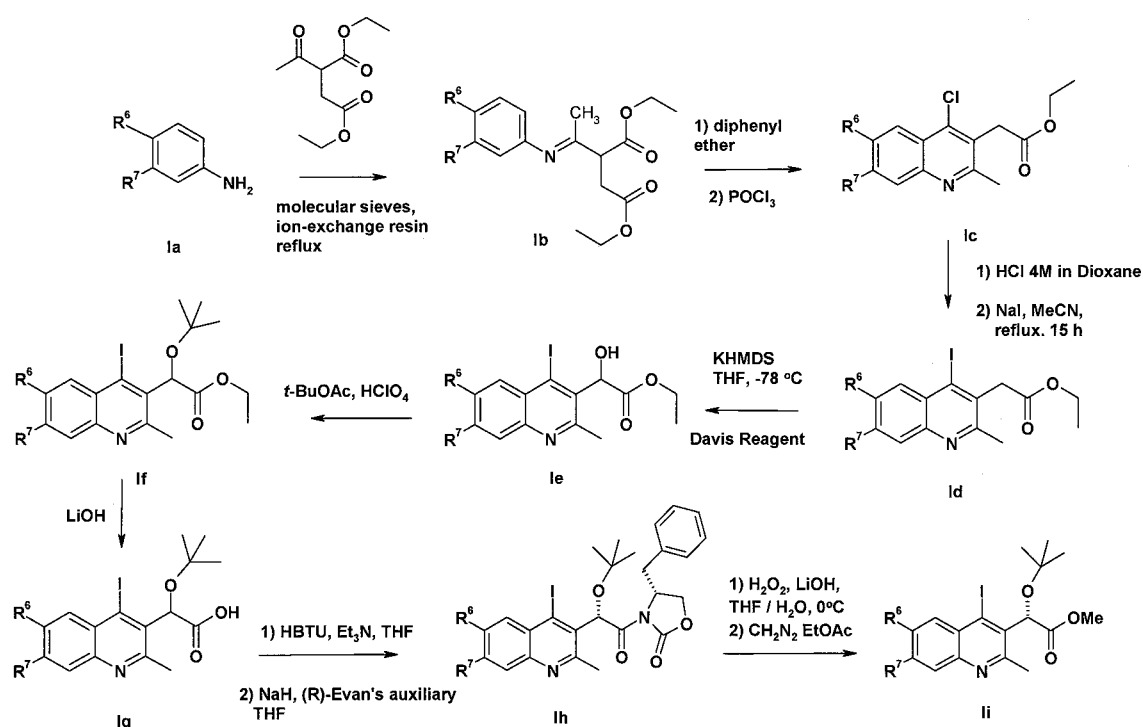


wherein  $W$  is iodo, bromo, chloro or OTf,  $R$  may be a substituent on the ring and  $P$  is as defined herein.

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

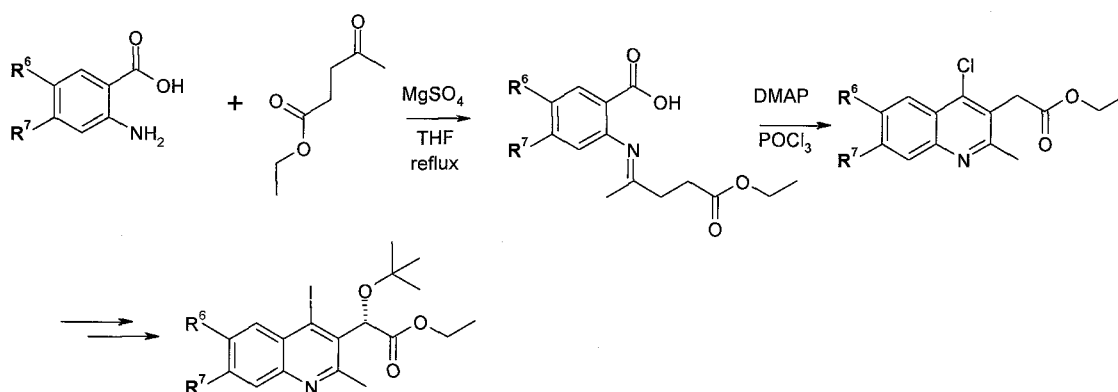
conditions. This intermediate is then cyclized under thermal conditions followed by halogenation of the resulting alcohol. The acetic acid ester side chain can be oxidized and protected to furnish the alpha t-butoxy acetic acid ester moiety as shown. Separation of the enantiomers can be accomplished by formation of diastereomers by addition of a chiral auxiliary such as an oxazolidinone followed by conversion to the corresponding ester by known means.

Scheme 1A



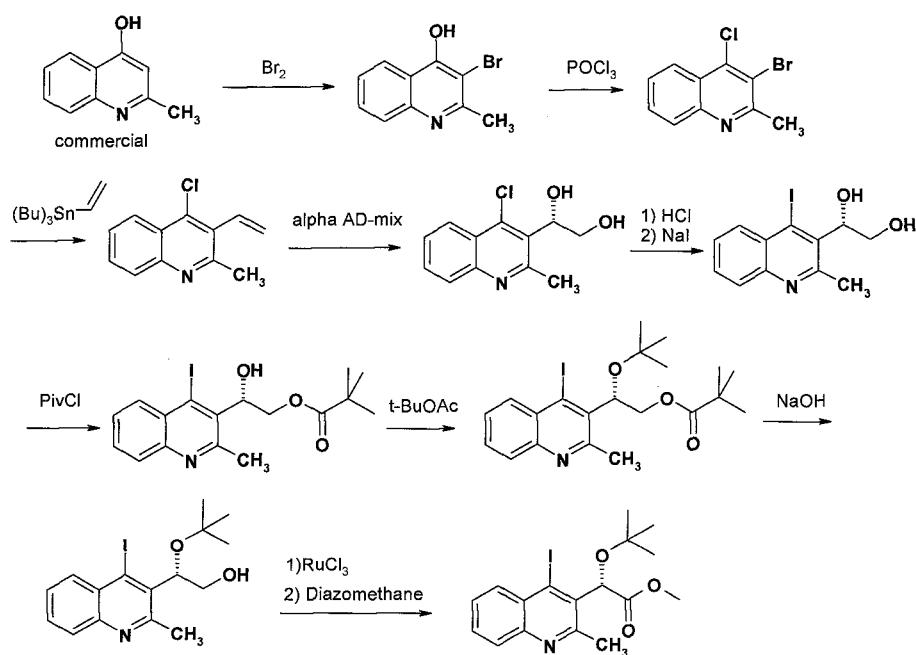
Alternatively, a modification of this approach can also be used to prepare the quinoline scaffold as shown in Scheme 2. In this method a properly substituted anthranilic acid derivative can be condensed under dehydration conditions with an appropriate ketone and subsequently cyclized under DMAP/POCl<sub>3</sub> conditions to the 4-chloroquinoline. Further elaboration can then be performed as outlined in Scheme 1A.

Scheme 2:

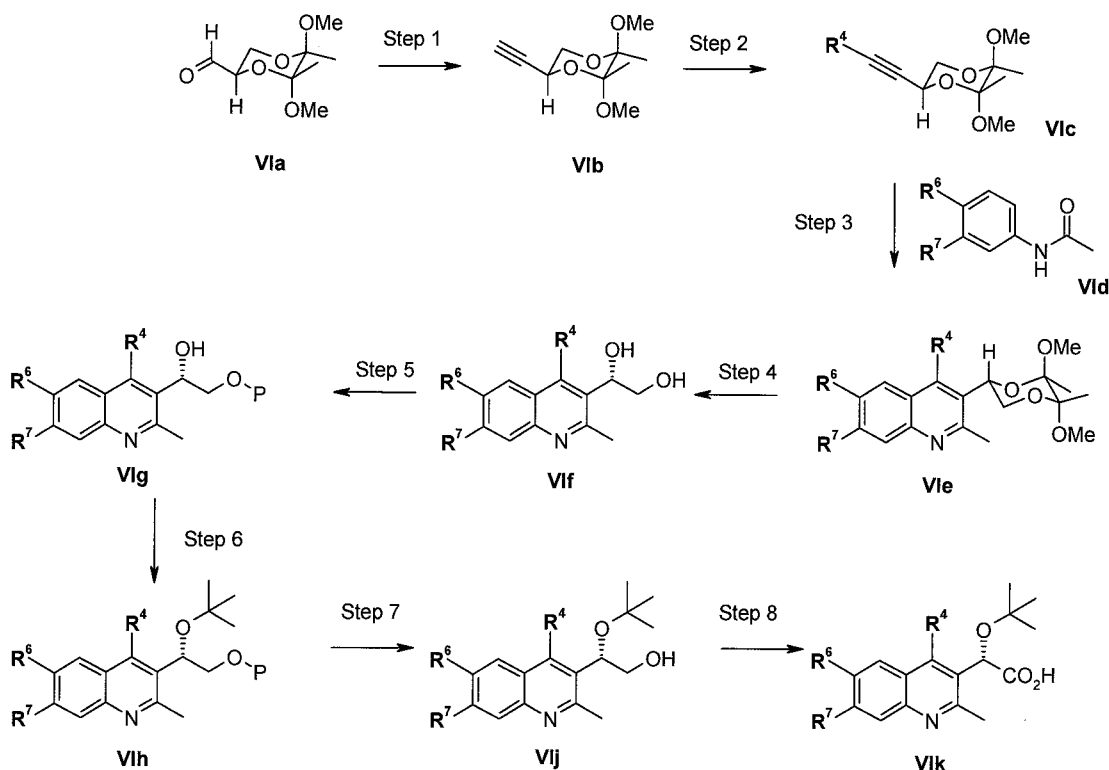


Furthermore, in an alternative route the quinoline scaffold can be accessed in an enantioselective manner as outlined in Scheme 3.

**Scheme 3:**



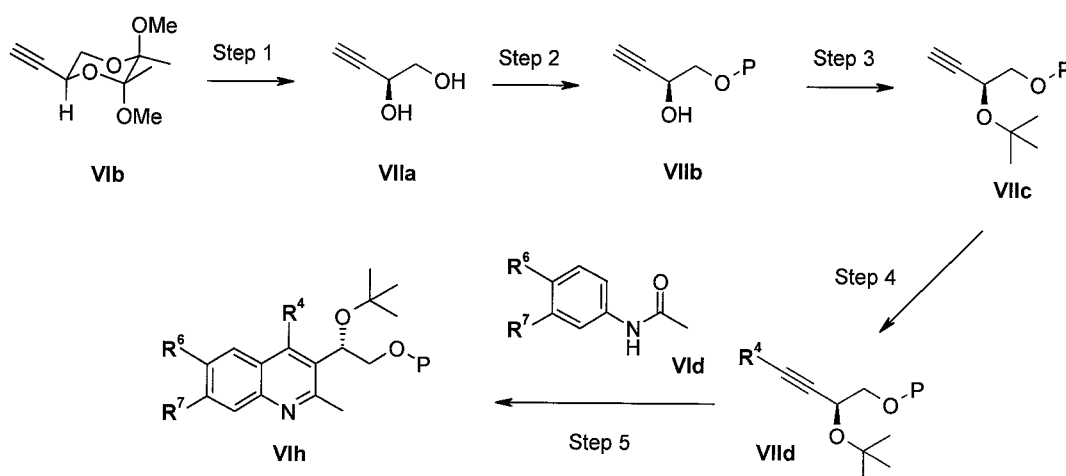
A quinoline precursor can be selectively brominated in the 3-position and subsequently elaborated into the chiral diol by standard methods known in the literature. The chiral diol can be differentially protected to the t-butyl ether followed by liberation of the primary alcohol. This alcohol can then 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, 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) to give the internal alkyne **VIc**. In this method a properly substituted benzoylacetone can be condensed in the presence of sulfur with an appropriate ketone or aldehyde by standard methods known in the literature. **VIc** then undergoes a cyclocondensation with amide **VIId** to give quinoline **VIe**. Those skilled in the art will recognize this may involve activation of amide **VIId** 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 **VIa** 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  $S_N1$  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**, 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  $S_N1$  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 **Vld**. The internal alkyne **Vld** then undergoes a cyclocondensation with amide **Vld** to give quinoline **Vlh**, 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 **Vlh**, the synthesis 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 ( $^{\circ}\text{C}$ ). Solution percentages and ratios express a volume to volume relationship, unless stated otherwise. Flash chromatography is carried out on silica gel ( $\text{SiO}_2$ ) 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 are purified using CombiFlash® Companion apparatus, purchased from Teledyne Isco Inc, employing pre-packed silica gel cartridges and EtOAc and hexanes 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 5 $\mu\text{M}$  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  $\mu\text{M}$ , 120 Å at 220 nM, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in  $\text{H}_2\text{O}$ ; solvent B is 0.06% TFA in  $\text{CH}_3\text{CN}$ ):

| 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<sub>2</sub>O: acetic anhydride;

Anti-his XL665: XL665 labeled anti-His antibody;

BOC or Boc: *tert*-butoxycarbonyl;

BSA: bovine serum albumin;

Bu: butyl;

CD: circular dichroism

DABCO: 1,4-diazabicyclo[2.2.2]octane

Db: dibenzylidene acetone;

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<sub>50</sub>: 50% effective concentration;

Eq: equivalent;

Et: ethyl;

Et<sub>3</sub>N : triethylamine;

Et<sub>2</sub>O: 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;

HEPES: N-2-hydroxyethyl piperazine N-ethane sulfonic acid;

HPLC: high performance liquid chromatography;

IC<sub>50</sub>: 50% inhibitory concentration;

ITC: Isothermal calorimetry;

<sup>i</sup>Pr or i-Pr: 1-methylethyl (*iso*-propyl);

K<sub>d</sub><sub>app</sub>: apparent affinity constant;

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-butyl lithium;

NMR: nuclear magnetic resonance spectroscopy;

OD: optical density;

ORD: optical rotary dispersion;

Ph: phenyl;

PhMe: toluene;

PG: protecting group;

PPh<sub>3</sub>: triphenylphosphine;

Pr: propyl;

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

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

SM: starting material;

Strep-EuK: Streptavidin labeled with europium cryptate;

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

TCEP: tris[2-carboxyethyl] phosphine;

Tf: trifluoromethanesulfonyl;

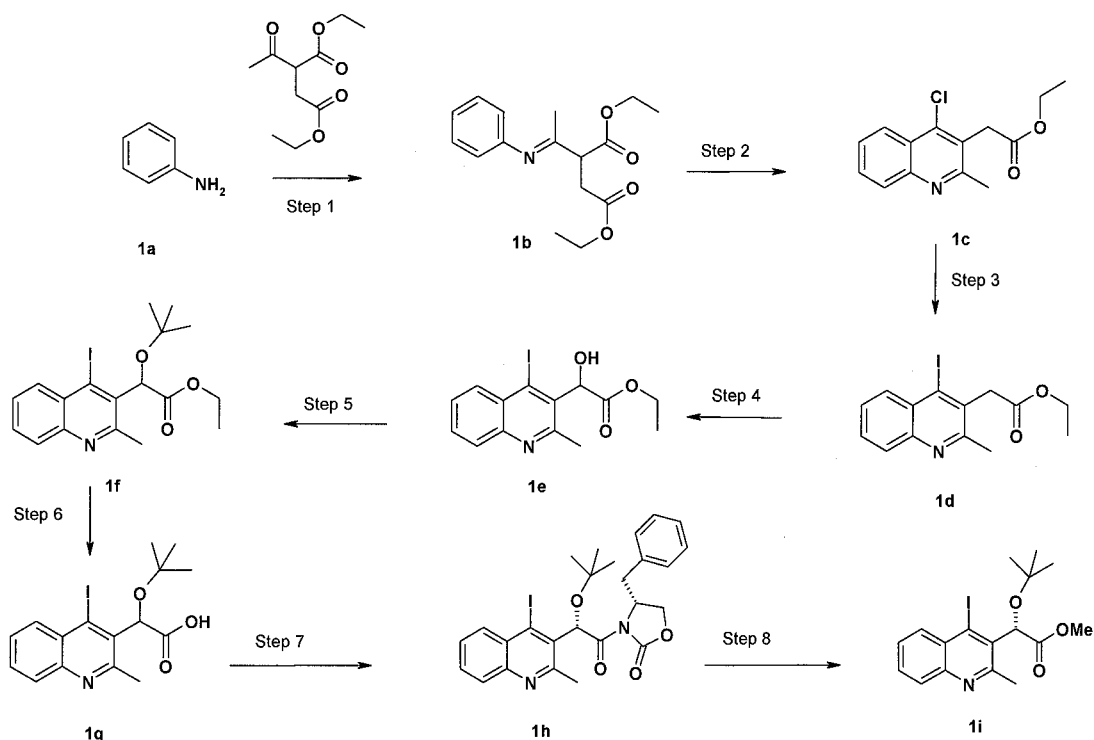
Tf<sub>2</sub>O: trifluoromethanesulfonic anhydride;

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 shows 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 reaches ~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<sub>2</sub>SO<sub>4</sub>, 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<sub>3</sub> (20 mL). The aqueous layer is extracted with DCM, and the combined organic layer is dried over anhydrous MgSO<sub>4</sub>, 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 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 this is stirred for an additional 30 min at -78°C. The reaction is quenched with saturated NH<sub>4</sub>Cl 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<sub>2</sub>SO<sub>4</sub>), 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<sub>3</sub> until pH ~ 6. The crude product is extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried over MgSO<sub>4</sub>, 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 DCM (3 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and dried under high vacuum to afford **1g** as a foamy solid (0.56 g, >98% yield).

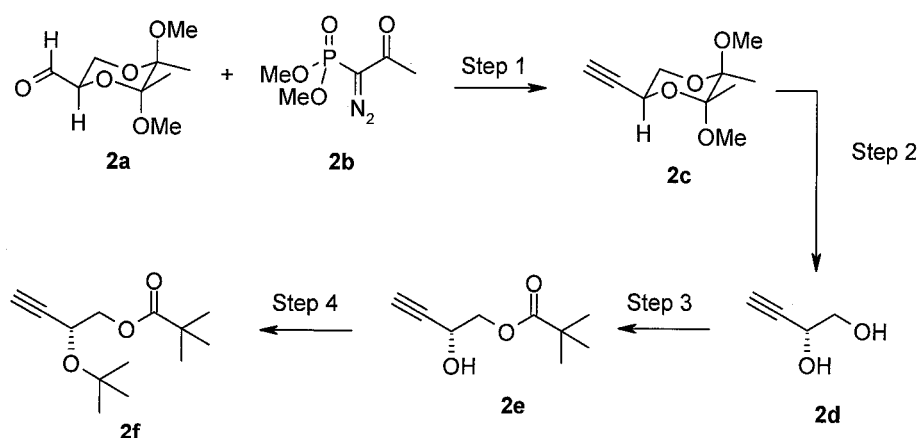
Step 7:

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<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>O (2 mL/1 mL) at 0°C is added H<sub>2</sub>O<sub>2</sub> (30%, 0.36 mL) followed by LiOH monohydrate (17 mg, 0.41 mmol) dissolved in water (1 mL). The reaction mixture is stirred at 0°C for 30 min at which time 10% Na<sub>2</sub>SO<sub>3</sub> (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, herein incorporated by reference), phosponate **2b** (6.6 g, 34 mmol) and K<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>O (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<sub>2</sub>SO<sub>4</sub> and concentrated to give alkyne **2c** (5.55 g, 97% yield).

**Step 2:**

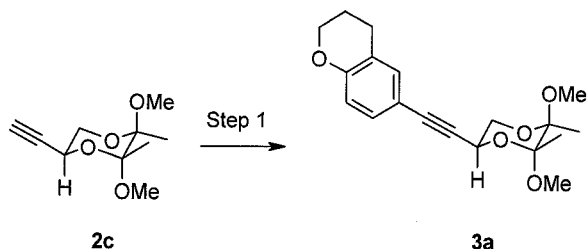
Alkyne **2c** (5.0 g, 25 mmol) is dissolved in TFA (35 mL) and water (3.6 mL) and the solution is stirred at RT. After 30 min, the reaction is concentrated under reduced pressure and the residue is purified by CombiFlash® Companion to give diol **2d** (1.8 g, 84% yield).

**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<sub>2</sub>. 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 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 (378 mg, 27% yield).

**Step 4:**

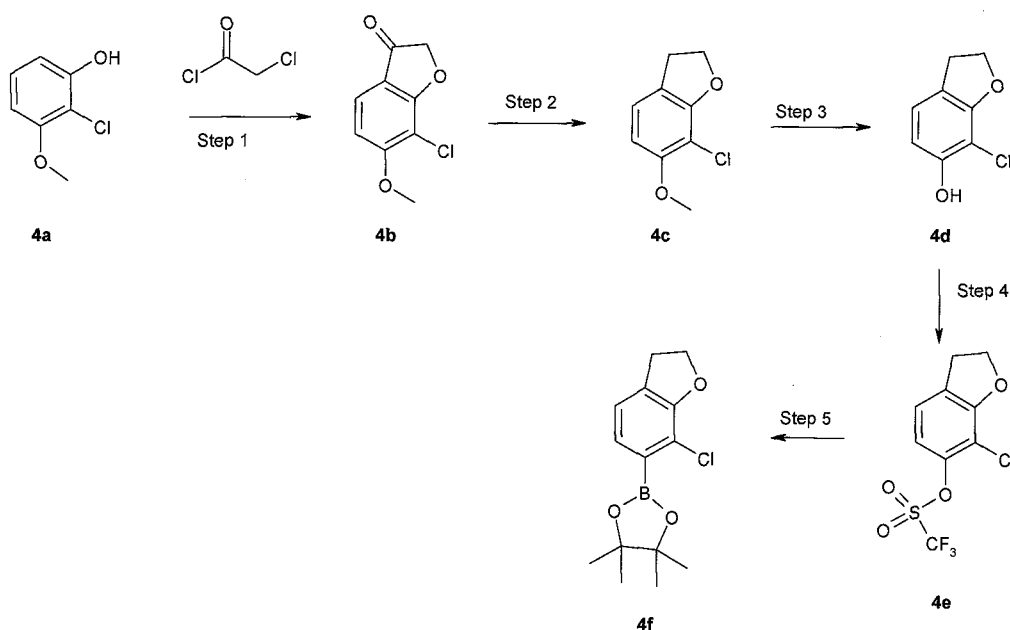
In a sealable reaction flask, a solution of the propargylic alcohol **2e** (375 mg, 2.20 mmol) and Amberlyst® H-15 resin (150 mg) in hexane (3 mL) is cooled to -78°C. Isobutene is then bubbled through the solution until the volume approximately doubles. The tube is then sealed, brought to RT and is stirred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

**Example 3: Synthesis of alkyne 3a****Step 1:**

Solid Pd(PPh<sub>3</sub>)<sub>4</sub> (444 mg, 0.385 mmol) and CuI (146 mg, 0.769 mmol) are

successively added to a solution of 6-iodochroman (10 g, 34 mmol) and alkyne **2c** (11 g, 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<sub>2</sub>SO<sub>4</sub> and the residue purified by CombiFlash® Companion to give alkyne **3a** (10.8 g, 84% yield).

**Example 4:** Synthesis of boronate fragment **4f** (used in preparation of 1086)



**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<sub>3</sub> (20.4 g, 152 mmol). As the AlCl<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub>, 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  $\mu$ L, 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  $\mu$ L, 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 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:

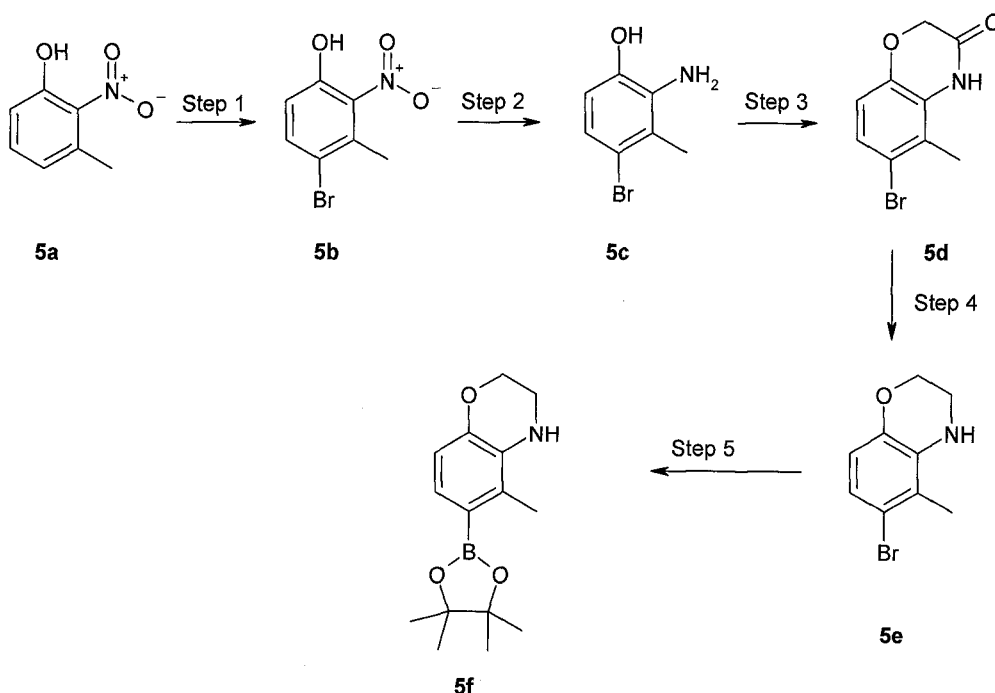
The phenol **4d** (40 mg, 0.23 mmol) is dissolved in DCM (2 mL), cooled to 0°C and treated with pyridine (95  $\mu$ L, 1.17 mmol), followed by  $Tf_2O$  (44  $\mu$ L, 0.26 mmol). The reaction is allowed to stir at this temperature for 10 min before warming to RT over a period of 1 h. The reaction mixture is diluted with DCM and the organic phase washed with 10% citric acid and then brine. The organic phase is dried over

anhydrous  $\text{MgSO}_4$ , 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)diborone (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  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  (27 mg, 0.03 mmol). The mixture is de-gassed a further 5 min before being heated to  $90^\circ\text{C}$  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  $\text{MgSO}_4$ , 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** (used in preparation of 1077, 1091, 1095, 1099, 1100, 1118)



#### 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  $0^\circ\text{C}$

before being poured into ice water (250 mL). The mixture is extracted with EtOAc (2 X 100 mL) and then washed with 5% NaHCO<sub>3</sub> (2 X 50 mL) before being dried over anhydrous MgSO<sub>4</sub>, 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<sub>2</sub> (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<sub>2</sub> (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<sub>3</sub>. 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<sub>4</sub>, 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  $\mu$ L, 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 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:

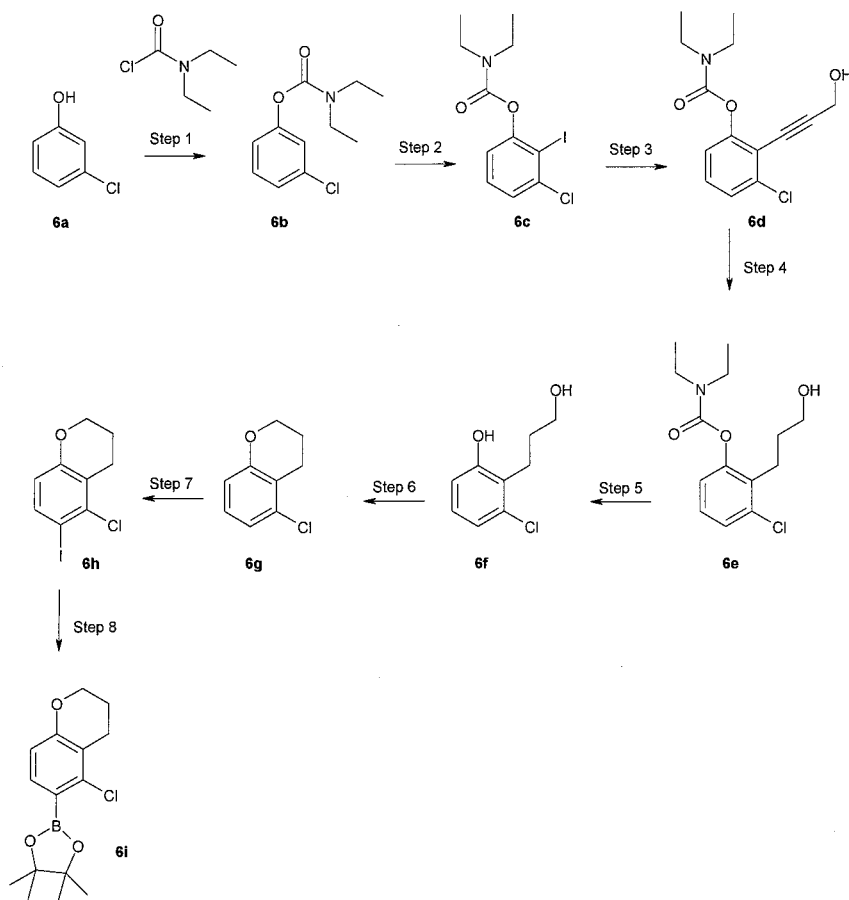
To an ice cold THF (6 mL) solution of the cyclic amide **5d** (280 mg, 1.16 mmol) under nitrogen, a borane-THF solution (1M in THF, 1.74 mL, 1.74 mmol) is added slowly. The reaction mixture is slowly allowed to warm to RT, then is stirred at RT for approximately 1.5 h and then gently heated to reflux 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  $\text{MgSO}_4$ , 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.  $\text{PdCl}_2(\text{dppf})\text{-DCM}$  (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  $\sim 90^\circ\text{C}$  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  $\text{MgSO}_4$ , 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** (used in preparation of 1038, 1039, 1053, 1054, 1055, 1056, 1083)

**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), is dried over anhydrous  $\text{MgSO}_4$ , 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 (200 mL), dry  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure to obtain **6c** (18.6 g, 39% yield).

Step 3:

The iodocarbamate **6c** (10 g, 28 mmol), propargyl alcohol (3.3 mL, 56 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (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  $100^\circ\text{C}$ . After 1 h, the reaction mixture is cooled to RT and poured into EtOAc (100 mL) and this mixture is extracted with 10% HCl (2 x 100 mL). The organic layer is dried over  $\text{MgSO}_4$  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  $\text{Rh-Al}_2\text{O}_3$  (5% w/w, 3.45 g, 1.68 mmol). The flask is evacuated and charged with 1 atmosphere of  $\text{H}_2$  (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  $\text{Et}_2\text{O}$  (3 x 100 mL), dried over  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure to obtain phenol **6f** (869 mg, 51% yield).

Step 6:

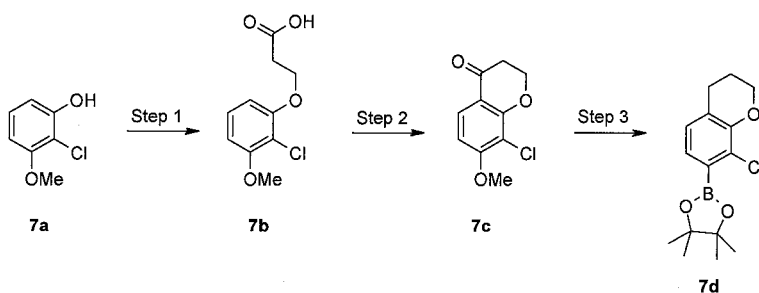
Diethyl azodicarboxylate (953  $\mu\text{L}$ , 6.05 mmol) is added dropwise to a solution of phenol **6f** (869 mg, 4.66 mmol) and  $\text{PPh}_3$  (1.59 g, 6.053 mmol) in THF (65 mL) and the reaction is stirred at RT. After 4 h, the reaction mixture is evaporated under reduced pressure. The residue is then purified by CombiFlash® Companion to obtain the chroman **6g** (387 mg, 49% yield).

**Step 7:**

Iodine (583 mg, 2.295 mmol) is added to a solution of chroman **6g** (387 mg, 2.29 mmol) and AgNO<sub>3</sub> (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<sub>4</sub>), 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(pinacolato)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<sub>2</sub>(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<sub>4</sub>, 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 (used in preparation of 1065, 1107)****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, MeOH (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<sub>2</sub>SO<sub>4</sub> 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.

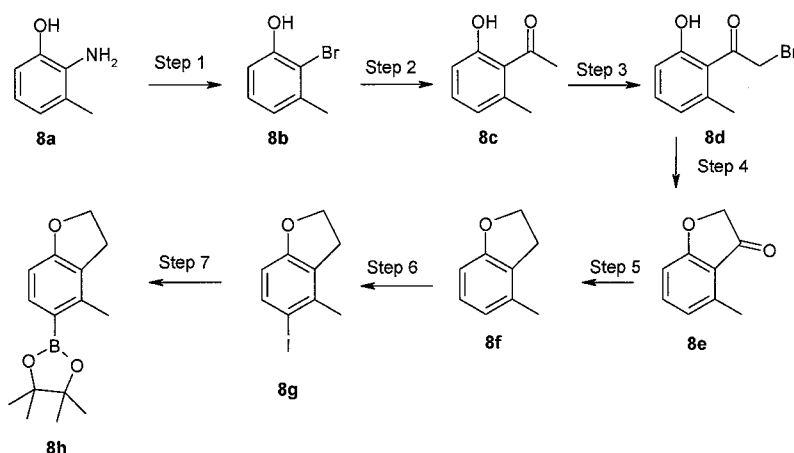
#### Step 2:

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, 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<sub>3</sub> (2 x 100 mL) and brine (75 mL). The organic phase is dried over anhydrous MgSO<sub>4</sub> and evaporated to give **7c** as a sticky violet solid which is used as such (1.29 g).

#### 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** (used in preparation of 1069)



#### Step 1

2-Amino-*m*-cresol **8a** (5.7 g, 46.3 mmol) is dissolved in H<sub>2</sub>O (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°C, and NaNO<sub>2</sub> in H<sub>2</sub>O (20 mL) is added over a period of 30 min. The stirring is continued for 15 min at 0°C, the mixture is then transferred in one shot to a stirring mixture of Cu(I)Br (7.64 g, 53.2 mmol) in H<sub>2</sub>O (20 mL) and HBr (48%, 17 mL, 0.31 mol) at 0°C (protected from light). The reaction is stirred for 15 min at 0°C, warmed to 60°C, 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<sub>4</sub>, 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<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> (766 mg, 1.09 mmol, 15 mol%) 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<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> (380 mg, 0.05 mol%) 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<sub>4</sub>, filtered and concentrated over silica to afford the mixture that is purified using the CombiFlash® Companion 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<sub>3</sub> (15 mL) before being treated with Cu(II)Br<sub>2</sub> (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.

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<sub>4</sub>, 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<sub>2</sub>O (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 dihydrobenzofuran **8f** (174 mg, 69% yield) as a colorless oil.

Step 6:

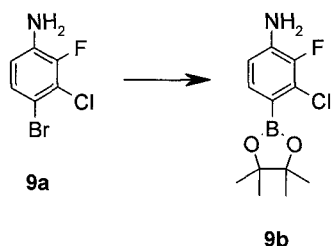
To a solution of the dihydrobenzofuran **8f** (240 mg, 1.8 mmol) in MeOH (5 mL), AgNO<sub>3</sub> (304 mg, 1.79 mmol) is added followed by iodine (453 mg, 1.79 mmol). The yellow mixture is stirred at RT for 1 h. To the reaction mixture is added a solution of 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> 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<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2x). The organic phase is dried over anhydrous MgSO<sub>4</sub>, 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(pinacolato)diborane (585 mg, 2.31 mmol), potassium acetate (511 mg, 5.4 mmol) in DMF (20 mL) is deoxygenated (Ar balloon and sonication for 5 min); then the catalyst (PdCl<sub>2</sub>dppf,

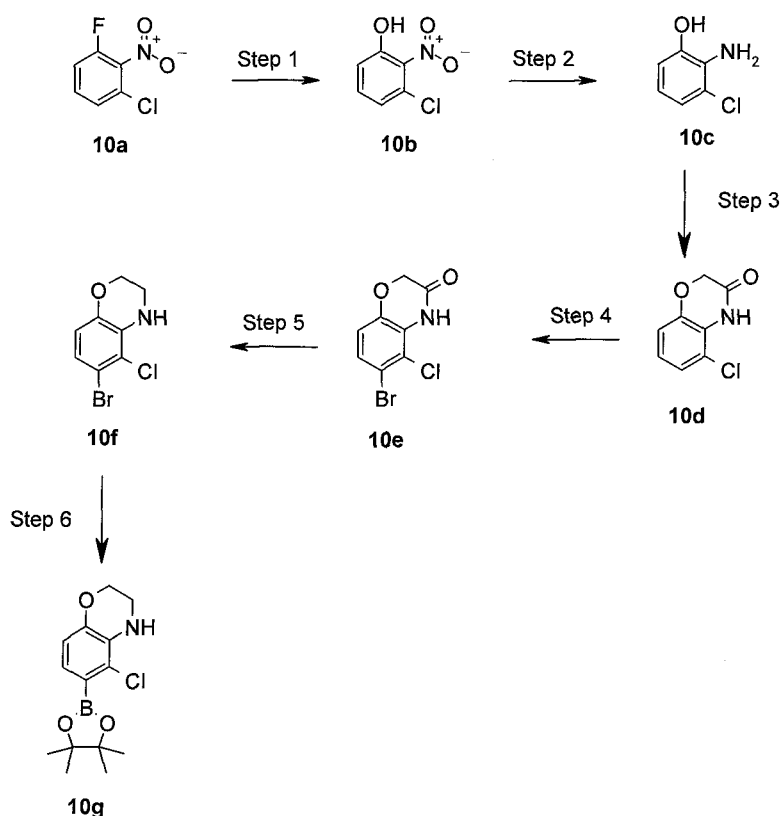
188 mg, 0.23 mmol) is added with additional degassing (Ar balloon and sonication for 2 min). The mixture is then heated to 95°C for 4 h. The mixture is cooled, EtOAc (200 mL) is added, washed with brine (3x), water (2x), dried over anhydrous MgSO<sub>4</sub>, filtered and solvent evaporation over silica 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** (used in Example 43)



Anhydrous DMF (60 mL) is added to a flask charged with bromide **9a** (5.00 g, 22.2 mmol), *bis*-(pinacolato)diborone (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<sub>2</sub> 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<sub>4</sub>, filtered and evaporated to a black syrup which is purified by flash column chromatography (EtOAc/hexanes) 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** (used in preparation of 1102, 1108, 1109, 1110, 1111, 1119, 1142)

**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<sub>2</sub>O<sub>2</sub> (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 (400 mL + 100 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<sub>2</sub> 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<sub>4</sub>, 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:

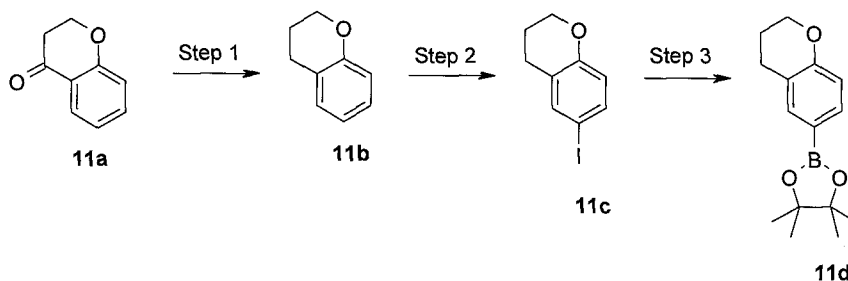
A solution of borane in THF (1.0 M, 18.5 mL, 18.5 mmol) is added dropwise to an ice-cold solution of lactam **10e** (4.00 g, 15.2 mmol) in anhydrous THF (75 mL), and the reaction is allowed to warm to RT. After 30 min, the solution is heated to gentle reflux under a N<sub>2</sub> atmosphere. After 2 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<sub>2</sub> 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<sub>4</sub>, 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** (used in preparation of 1006, 1021, 1022)



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:

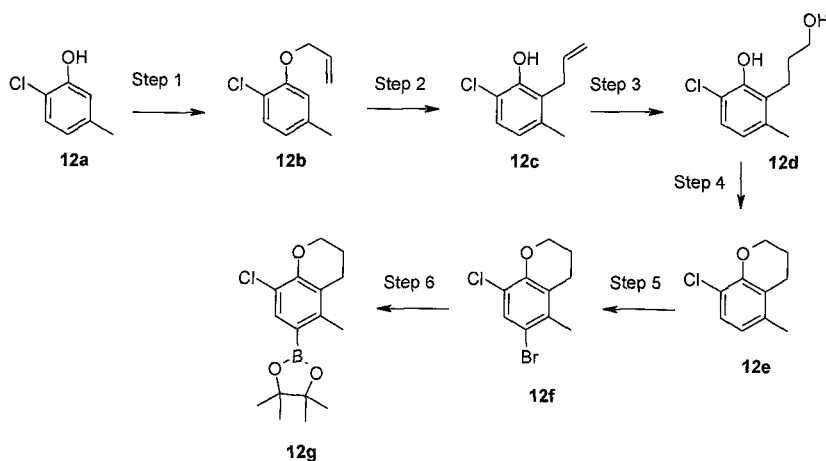
AgNO<sub>3</sub> (12.0 g, 70.6 mmol) and I<sub>2</sub> (15.8 g, 62.3 mmol) are added sequentially to a solution of **11b** (8.45 g, 63.0 mmol) dissolved in MeOH (225 mL). The reaction is allowed to stir for 1 h, filtered on Celite® and the filtrate concentrated under reduced

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  $\text{Na}_2\text{SO}_4$ , 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[pinacolato]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  $\text{PdCl}_2\text{dppf}$ -DCM complex (314 mg, 0.38 mmol). The reaction mixture is then degassed for an additional 5 min before being heated to  $95^\circ\text{C}$  for 5 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 100 mL). The combined organics are washed with water (100 mL) and brine (100 mL). The organic phase is then dried over  $\text{MgSO}_4$  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** (used in preparation of 1037, 1042)



### 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<sub>2</sub>O (3 x 500 mL). The organic layer is dried over MgSO<sub>4</sub>, 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) 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<sub>2</sub>O<sub>2</sub> (104 mL, 916 mmol, 20 eq). 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<sub>4</sub> and concentrated. The crude product is purified by CombiFlash® Companion to give **12d** (7.1g, 77% yield).

Step 4:

To a solution of the diol **12d** (7.1 g, 35.3 mmol) in THF (500 mL), PPh<sub>3</sub> (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).

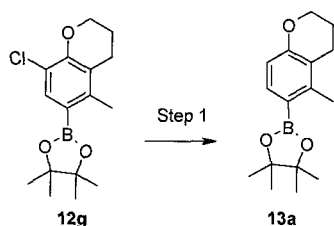
Step 5:

The chroman derivative **12e** (5.26 g, 28.8 mmol) is dissolved in AcOH (70 mL) and is then treated with Br<sub>2</sub> 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<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (25 mL) and saturated NaHCO<sub>3</sub> (25 mL). The organic layer is dried over MgSO<sub>4</sub>, concentrated and purified by CombiFlash® Companion to obtain the desired product **12f** (2.7 g, 36% yield).

**Step 6:**

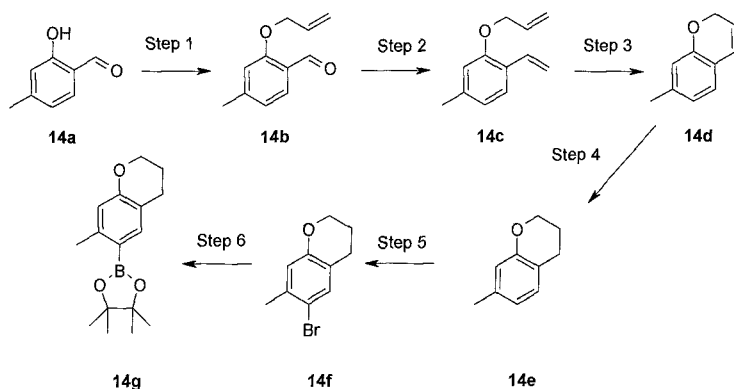
The bromide **12f** (2.71 g, 10.4 mmol) is dissolved in DMF (120 mL) and treated with bispinocolatoborane (4 g, 15.5 mmol) and potassium acetate (3.45 g, 36.3 mmol). The mixture is degassed (using an Ar balloon) before the introduction of the catalyst (PdCl<sub>2</sub>dppf, 845 mg, 1.04 mmol). The mixture 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<sub>2</sub>O (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<sub>4</sub>, 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** (used in preparation of 1043, 1044, 1090, 1092, 1096, 1122)

**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<sub>4</sub> and concentrated to obtain boronic ester **13a** (0.78 g, 97% yield).

**Example 14:** Synthesis of boronate fragment **14g** (used in preparation of 1017)

**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<sub>2</sub>SO<sub>4</sub> and concentrated. The product is then purified by CombiFlash® Companion in two batches (120 g column) 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<sub>2</sub>SO<sub>4</sub> and concentrated. The crude yellow liquid is then taken up in EtOAc (1 mL) and diluted with hexanes (20 mL), after which Ph<sub>3</sub>PO 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<sub>2</sub> (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<sub>2</sub> 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 purified by CombiFlash® Companion to provide chroman **14e** (800 mg, 84% yield).

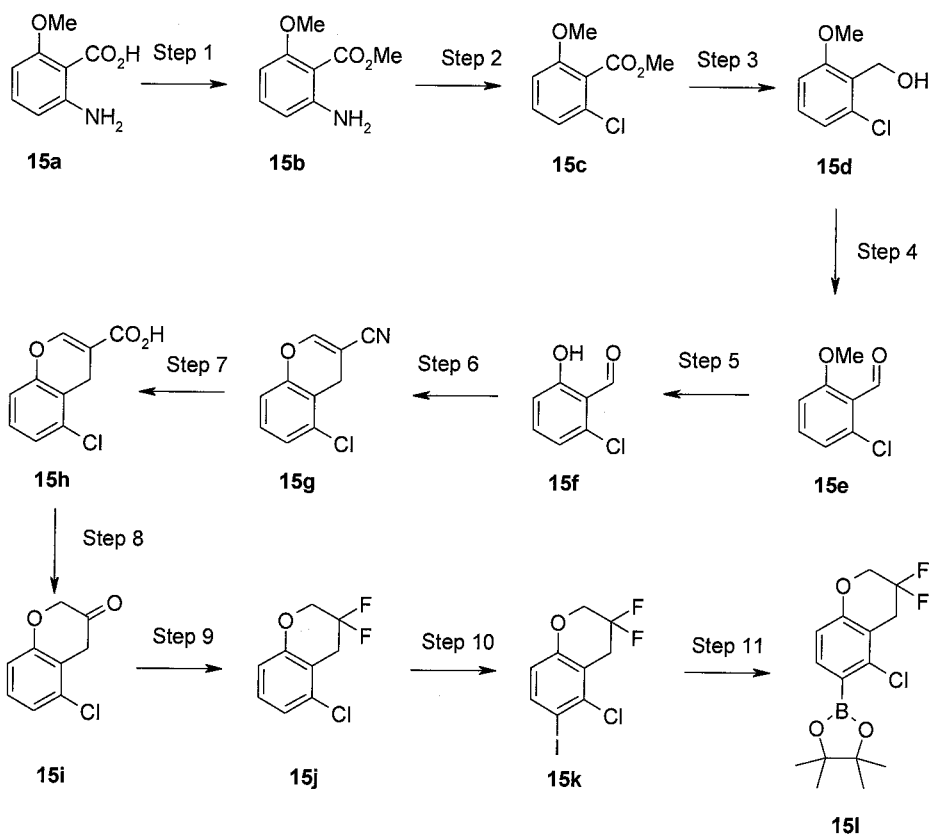
Step 5:

Neat Br<sub>2</sub> (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<sub>3</sub> (2 x 50 mL). The organic layer is dried over Na<sub>2</sub>SO<sub>4</sub> 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<sub>2</sub>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 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<sub>2</sub>SO<sub>4</sub>, 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 **15I** (used in preparation of 1098)

**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<sub>2</sub> (10 g) and the product purified by CombiFlash® Companion to yield ester **15b** (5.2 g, 95% yield).

**Step 2:**

A solution of NaNO<sub>2</sub> (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<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> and 0.5 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (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<sub>3</sub> (100 mL). The combined organic phases are then dried over MgSO<sub>4</sub> 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<sub>2</sub>Cl<sub>2</sub> (20 mL) is added slowly to a precooled (-30 °C) solution of BBr<sub>3</sub> (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<sub>3</sub> and then brine (25 mL each). The organic layer is dried over MgSO<sub>4</sub>, 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<sub>4</sub> 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<sub>3</sub> (2 x 100 mL), water (2 x 100 mL) and brine (100 mL). The organic layer is dried over MgSO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub> (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 (Caution! Exothermic!) addition of saturated NaHCO<sub>3</sub> (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<sub>4</sub>, filtered and concentrated. The product is purified by CombiFlash® Companion to provide difluorochroman **15j** (225 mg, 71% yield).

Step 10:

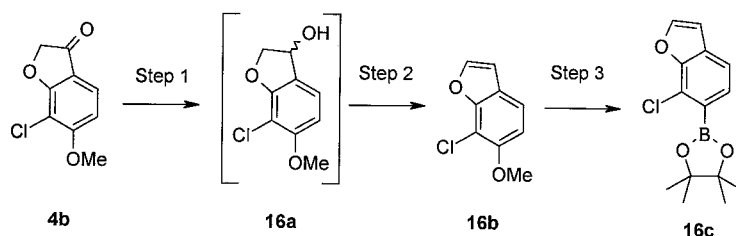
Solid silver nitrate (187 mg, 1.1 mmol) and iodine (279 mg, 1.1 mmol) are added successively to a solution of difluorochroman **15j** (225 mg, 1.1 mmol) dissolved in MeOH (7.8 mL). The reaction is stirred at RT for 90 min and then filtered through a pad of Celite®. The filtrate is treated with a drop of 0.5 N Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (orange color

dissipated) then concentrated under reduced pressure. The residue is partitioned between H<sub>2</sub>O, 0.5N Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> 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<sub>4</sub>, 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[pinacolato]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<sub>2</sub>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 approximately 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<sub>4</sub> 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** (used in preparation of 1088)



#### Step 1:

Solid NaBH<sub>4</sub> (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<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford alcohol **16a** (1.52 g >99% yield). This material is used as is in the next step.

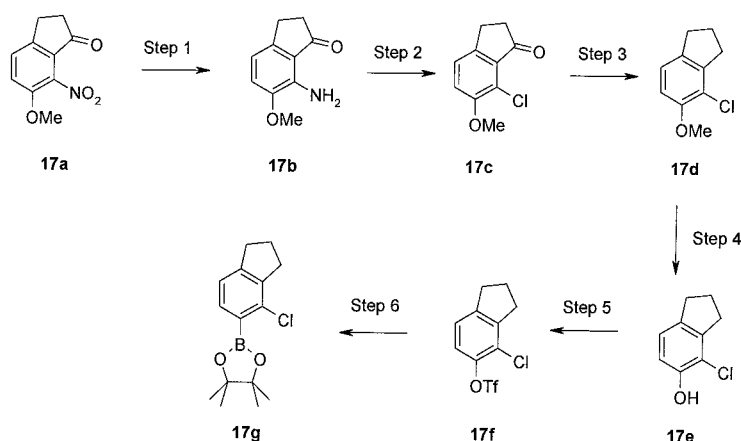
#### Step 2:

TFA (2.9 mL) is added dropwise to a solution of crude alcohol **16a** (1.5 g; 7.47 mmol) in  $\text{CH}_2\text{Cl}_2$  (28 mL) at  $0^\circ\text{C}$ . The solution is stirred for 30 min, and then concentrated to dryness. The residue is taken up in EtOAc, washed with  $\text{NaHCO}_3$  (saturated), brine, dried over  $\text{Na}_2\text{SO}_4$ , 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** (used in preparation of 1047, 1048, 1049)



### 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  $100^\circ\text{C}$  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 to afford aniline **17b** (3.06 g, 72% yield) as a yellow solid.

### Step 2:

A solution of  $\text{NaNO}_2$  (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  $0^\circ\text{C}$ . The resulting mixture is stirred at this temperature for 1 h. Solid  $\text{CuCl}$  (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<sub>4</sub>, filtered and evaporated to dryness. The product is purified by CombiFlash® Companion 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 to afford indane **17d** (902 mg, 88% yield) as a white crystalline solid.

#### Step 4:

A solution of BBr<sub>3</sub> 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 1.5 h, water (50 mL) is added (caution! Exothermic!) and the mixture is extracted with DCM (3 x 50 mL). The combined organic layers are dried over MgSO<sub>4</sub>, 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:

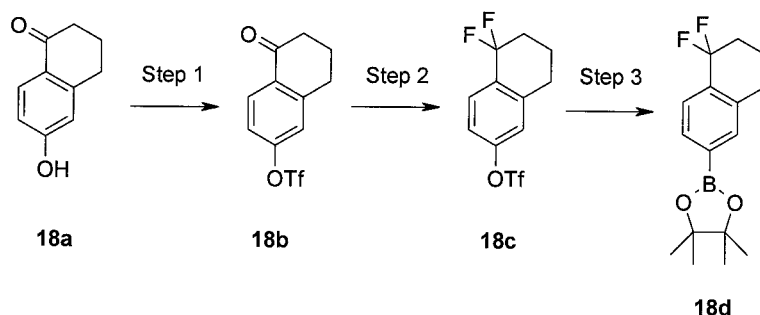
Tf<sub>2</sub>O (1.05 mL, 12 mmol) is added to a precooled (0°C) solution of phenol **17e** (700 mg, 4.1 mmol) and Et<sub>3</sub>N (1.7 mL, 12 mmol) in DCM (20 mL). The resulting dark solution is allowed to warm to RT. After 25 min, the reaction is quenched with saturated NaHCO<sub>3</sub> (10 mL), diluted with DCM, and the organic layer washed with water, brine, dried over MgSO<sub>4</sub> and evaporated to dryness. The product is purified by CombiFlash® Companion 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<sub>2</sub>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<sub>4</sub> and filtered and concentrated. The crude mixture is further purified by CombiFlash® Companion to afford boronic ester **17g** (593 mg, 53% yield) as a pale yellow solid.

**Example 18:** Synthesis of boronate fragment **18d** (used in preparation of 1067)



**Step 1:**

Neat Tf<sub>2</sub>O (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<sub>4</sub>, filtered and concentrated. The product is purified by CombiFlash® Companion to give triflate **18b** (500 mg, 94% yield).

**Step 2:**

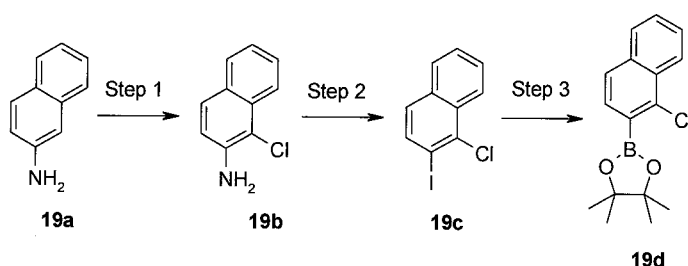
Deoxyfluor® (0.83 mL, 4.2 mmol) followed by EtOH (10 uL, 0.2 mmol) are added to neat triflate **18b** (500 mg, 1.7 mmol) in a sealable tube. The tube is sealed and the reaction is heated in an oil bath at 85°C and is stirred overnight. The reaction is then cooled to 0°C and quenched by the slow addition of NaHCO<sub>3</sub> (100 µL, CAUTION! 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<sub>4</sub>, filtered and concentrated. The crude product is purified by CombiFlash® Companion to provide the

difluorotetrahydronaphthyl 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** (used in preparation of 1070, 1078)



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  $\text{CCl}_4$  (150 mL). The reaction is then heated to  $50^\circ\text{C}$  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  $\text{MgSO}_4$  and evaporated to dryness to provide chloroaniline **19b** (2.8 g, 96% yield).

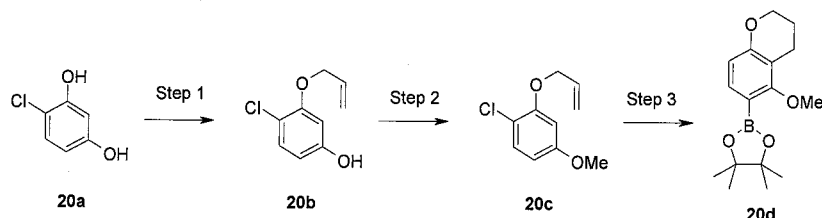
Step 2:

A solution of  $\text{NaNO}_2$  (1.2 g, 17 mmol) in water (5 mL) is slowly added to a precooled ( $0^\circ\text{C}$ ) 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  $5^\circ\text{C}$ . 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  $\text{Et}_2\text{O}$  (3 x 100 mL) and the combined organic layers washed successively with 3 N NaOH (2 x 50 mL), 5%  $\text{NaHSO}_3$  (50 mL) and brine (100 mL). The organic phase is dried over  $\text{MgSO}_4$ , 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** (used in preparation of 1064)



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  $\text{MgSO}_4$  and concentrated to dryness. The crude product is purified by CombiFlash® Companion to obtain allyl ether **20b** (1.8 g, 40% yield).

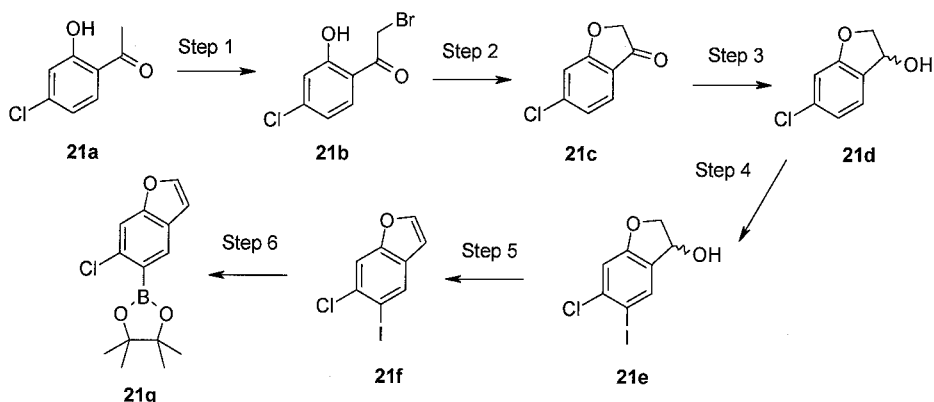
Step 2:

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  $\text{MgSO}_4$  and concentrated to dryness. The crude product is purified by CombiFlash® Companion to obtain methyl ether **20c** (1.8 g, 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** (used in preparation of 1071)

**Step 1:**

Solid  $\text{CuBr}_2$  (7.9 g; 35 mmol) is added to a solution of **21a** (4.0 g, 23 mmol) dissolved in EtOAc (32 mL) and  $\text{CHCl}_3$  (32 mL). The mixture is heated to reflux and is stirred for 8 h.  $\text{CuBr}_2$  (3.9 g, mmol) 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  $\text{MgSO}_4$ , 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  $\text{NaBH}_4$  (270 mg, 7.1 mmol) is added to a precooled ( $0^\circ\text{C}$ ) 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 ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to afford the crude alcohol **21d** (1.0 g), which is used directly in the next step.

**Step 4:**

Solid  $\text{AgNO}_3$  (1.0 g, 6.1 mmol) followed by  $\text{I}_2$  (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<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (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 (50 mL), brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to afford aryl iodide **21e** (1.6 g), which is used directly in the next step.

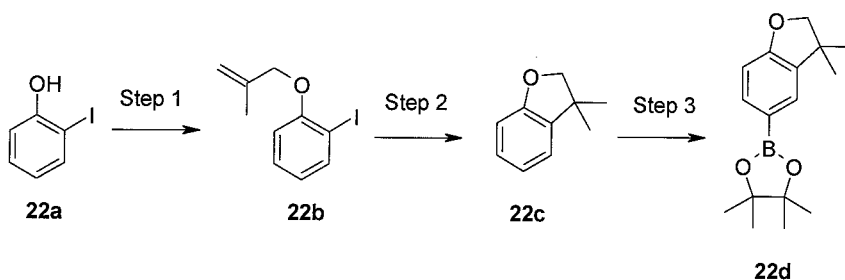
Step 5:

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<sub>3</sub> (50 mL) and brine (50 mL). The organic layer is dried over Na<sub>2</sub>SO<sub>4</sub>, 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** (used in preparation of 1068)



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:

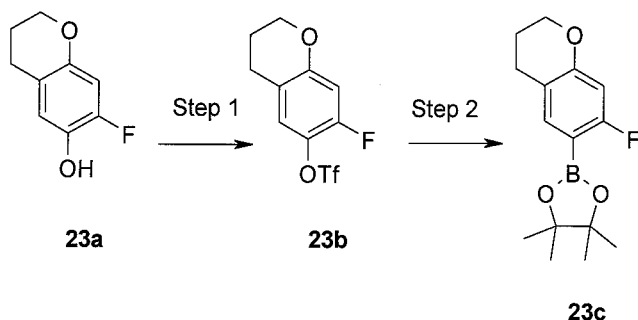
Neat tributyltin hydride (2.3 mL, 8.8 mmol) is added to a solution of aryl iodide **22b**

(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<sub>2</sub>. 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** (used in preparation of 1040, 1041, 1057)



### Step 1:

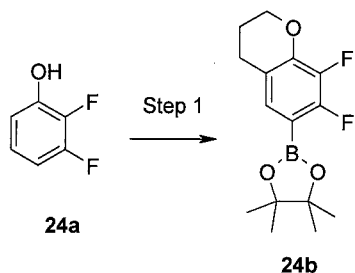
Neat Tf<sub>2</sub>O (056 mL, 3.3 mmol) is added dropwise to a cooled (0°C) solution of phenol **23a** (350 mg, 2.1 mmol; prepared according to Doi *et al Bull. Chem. Soc. Jpn.* **2004** 77, 2257-2263) and pyridine (0.91 mL, 11 mmol) in DCM (10 mL) under an Ar atmosphere. The reaction is allowed to warm to RT and then is stirred for about 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<sub>4</sub>, 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** (510 mg, 1.7 mmol), bis[pinacolato]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<sub>2</sub>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<sub>4</sub>, filtered and concentrated. The crude mixture is further purified by CombiFlash® Companion to afford boronic ester **23c** (200 mg, 42% yield).

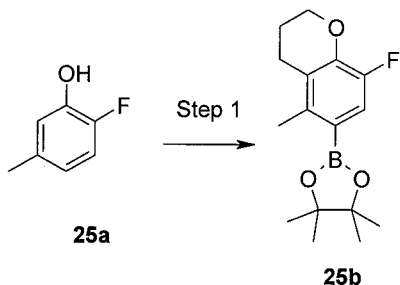
**Example 24:** Synthesis of boronate fragment **24b** (used in preparation of 1061)



Step 1:

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

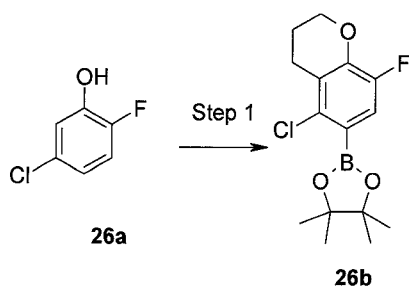
**Example 25:** Synthesis of boronate fragment **25b** (used in preparation of 1059)



Step 1:

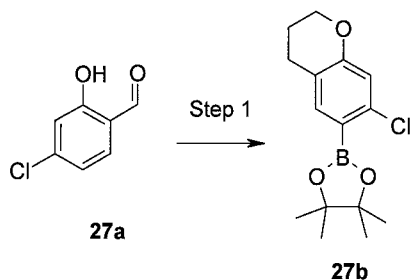
Compound **25b** is prepared from **25a** following a synthetic sequence identical to steps 1 to 6 of Example 12.

**Example 26:** Synthesis of boronate fragment **26b** (used in preparation of 1105, 1106)

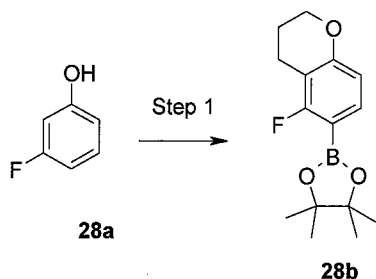


Step 1:

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

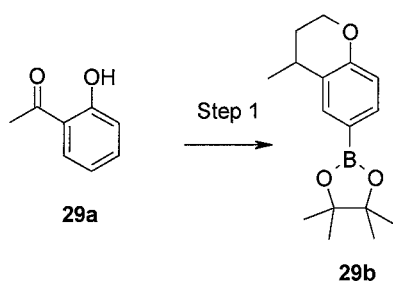
**Example 27:** Synthesis of boronate fragment **27b** (used in preparation of 1033)Step 1:

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** (used in preparation of 1060)Step 1:

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

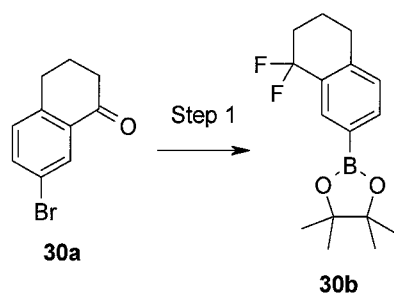
**Example 29:** Synthesis of boronate fragment **29b** (used in preparation of 1052)



Step 1:

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

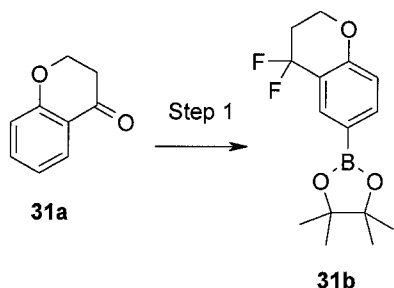
**Example 30:** Synthesis of boronate fragment **30b** (used in preparation of 1080)



Step 1:

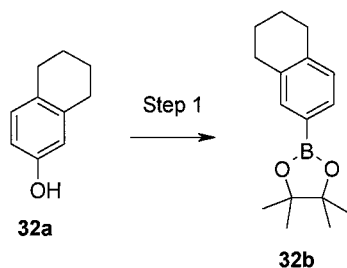
Compound **30b** is prepared from **30a** following a synthetic sequence identical to steps 2 and 3 of Example 18.

**Example 31:** Synthesis of boronate fragment **31b** (used in preparation of 1013)

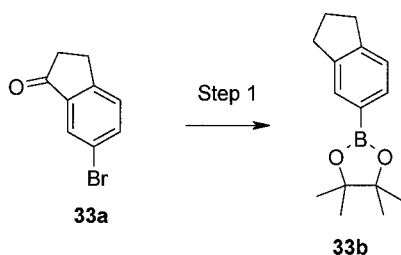


Step 1:

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

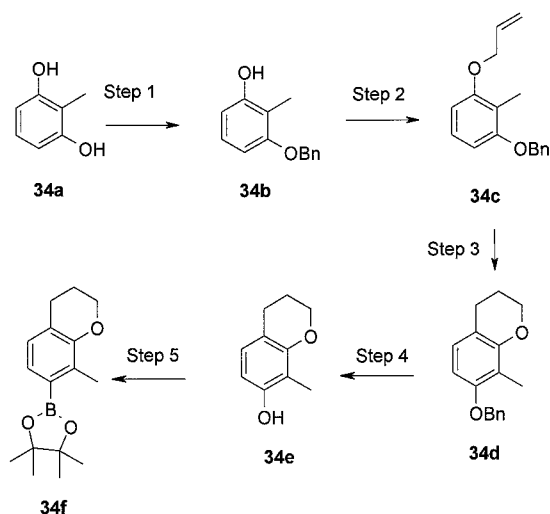
**Example 32:** Synthesis of boronate fragment **32b** (used in preparation of 1005)Step 1:

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** (used in preparation of 1023, 1034)Step 1:

Compound **33b** is prepared from **33a** following a synthetic sequence identical to steps 1 and 3 of Example 11.

**Example 34:** Synthesis of boronate fragment **34f** (used in preparation of 1094)

**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<sub>2</sub>SO<sub>4</sub> 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<sub>2</sub>SO<sub>4</sub> 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:**

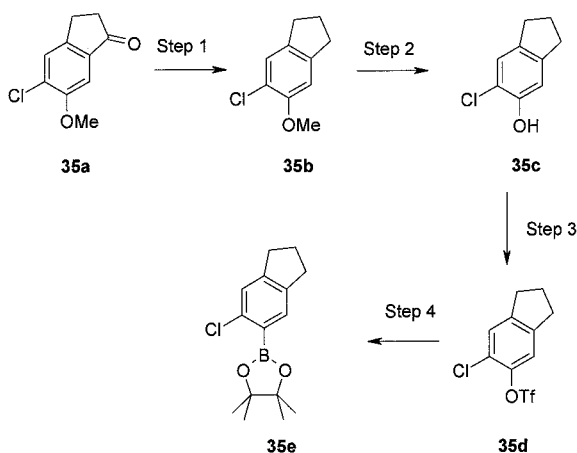
Benzyl ether **34d** and Pd-C (10% w/w, 100 mg, 0.094 mmol) are combined in EtOAc (5 mL) and the flask is evacuated and backfilled with a H<sub>2</sub> atmosphere (balloon).

After stirring for 3 h, the reaction is filtered through Celite® (EtOAc washing) and the filtrate concentrated to give phenol **34e** (145 mg, 95% yield).

**Step 5:**

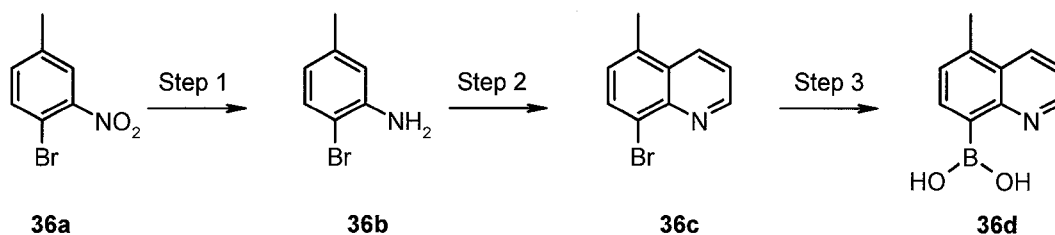
Compound **34f** is prepared from **34e** following a synthetic sequence identical to steps 5 to 6 of Example 17.

**Example 35: Synthesis of boronate fragment 35e (used in preparation of 1047)**



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

**Example 36: Synthesis of boronate fragment 36d (used in preparation of 1075, 1076)**



**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. 50 mL of 5% aqueous NaHCO<sub>3</sub> 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<sub>2</sub>CO<sub>3</sub> (20 mL) followed by 2.5 M aqueous NaOH (20 mL). The dark brown organic solution is then stirred with MgSO<sub>4</sub> 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:

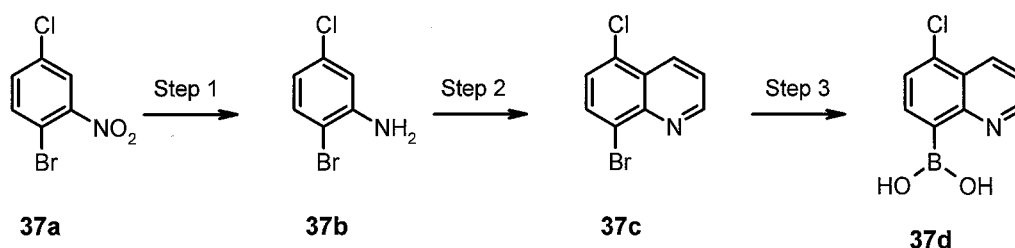
A mixture of compound **36b** (3.3 g, 17.7 mmol), glycerin (3.3 g, 35.5 mmol), nitrobenzene (2.2 g, 17.7 mmol) and 75% aqueous sulfuric acid (10 mL, 138 mmol) is stirred at 150°C for 3 h (mixture turns black and viscous). The reaction mixture is cooled down, poured into ice-water (200 mL) and 10 N aqueous 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<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give 4.8 g of a brown-red oil. This material is chromatographed on 80 g silica gel column (CombiFlash® Companion apparatus, hexanes-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<sub>2</sub>O (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<sub>2</sub>O. The aqueous layer is then transferred into a 500 mL Erlenmeyer flask and the pH of the solution is adjusted to approximately 6.3 (measured with a pH meter) by slowly adding a saturated solution of NaHCO<sub>3</sub> 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<sub>2</sub>O /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<sub>3</sub>CN/H<sub>2</sub>O 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** (used in preparation of 1084)



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<sub>2</sub>O is used for the extractions instead of EtOAc.

Step 2:

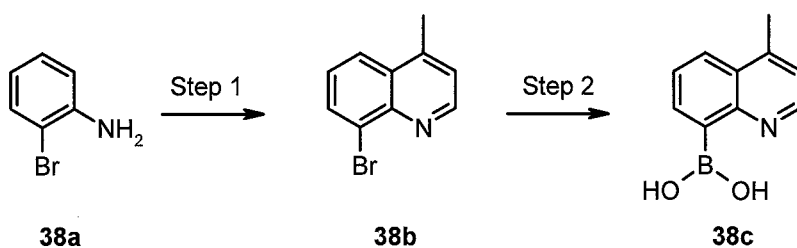
Compound **37b** (4.2 g, 20.3 mmol) is melted at 50°C in a 100 mL round-bottomed flask containing a stirring bar and immersed in an oil bath. A solution of zinc chloride (700 mg, 5.03 mmol) and ferric chloride (540 mg, 3.25 mmol) in water (3.3 mL) is added in one portion followed by absolute EtOH (20 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 CH<sub>2</sub>Cl<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts are washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under vacuum to give 3.69 g of a brown solid. This solid is triturated in hot CH<sub>3</sub>CN and filtered. The solid is discarded and the filtrate is concentrated under vacuum to give 2.3 g of a brown semi-solid. 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** (used in preparation of 1085)



Step 1:

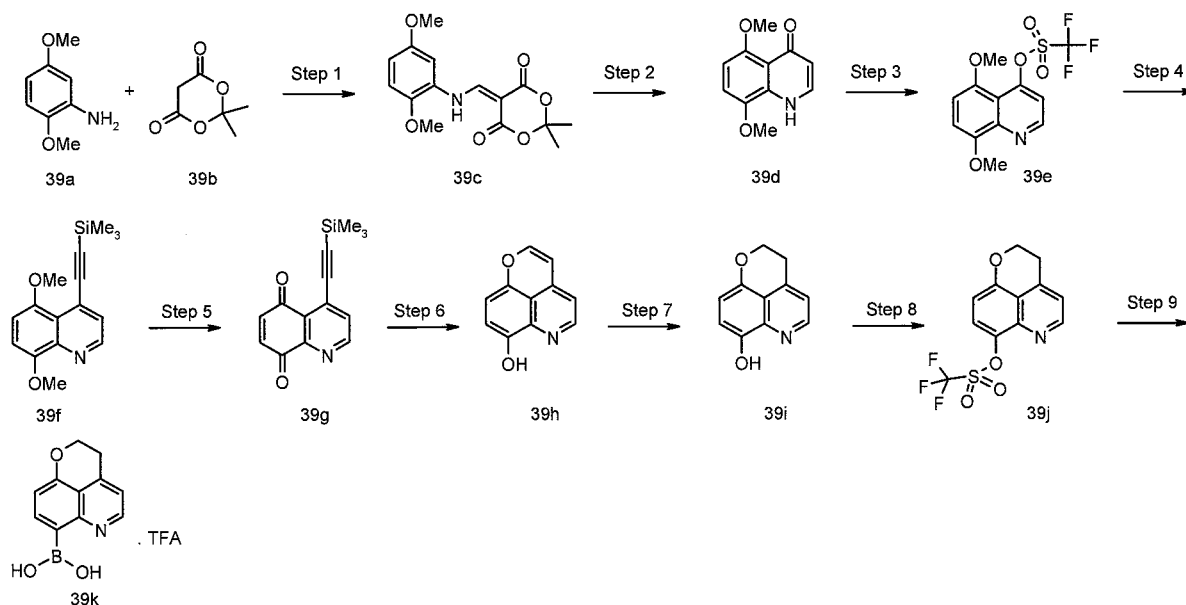
2-bromoaniline **38a** is transformed to compound **38b** using the procedure of example **37c** except that methyl vinyl ketone is used instead of acrolein.

Step 2:

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

**Example 39:** Synthesis of boronate fragment **39k** (used in preparation of 1131 and

in example 46)



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 taken 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 forms 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<sub>2</sub>O (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<sub>2</sub>O and brine and dried (Na<sub>2</sub>SO<sub>4</sub>). 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, 71% 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, 88.5 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<sub>2</sub>O and brine. After drying on Na<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>O (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 CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts are combined, washed with H<sub>2</sub>O, brine and dried (Na<sub>2</sub>SO<sub>4</sub>). 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<sub>2</sub>O is added and the solution is washed with EtOAc. The aqueous layer is neutralized with a saturated aqueous solution of NaHCO<sub>3</sub> and is extracted with EtOAc. The combined

organic extracts are washed with H<sub>2</sub>O, brine and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent is removed under reduced pressure to afford compound **39h** as a brown solid (250 mg, 19% yield).

Step 7:

Compound **39h** (230 mg, 1.24 mmol) is dissolved in absolute EtOH (11 mL) and 10% palladium on carbon is added (10% w/w, 23 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<sub>3</sub> mixture. The solvent is removed under reduced pressure to give compound **39i** as a brown sticky solid (200 mg, 86% yield).

Step 8:

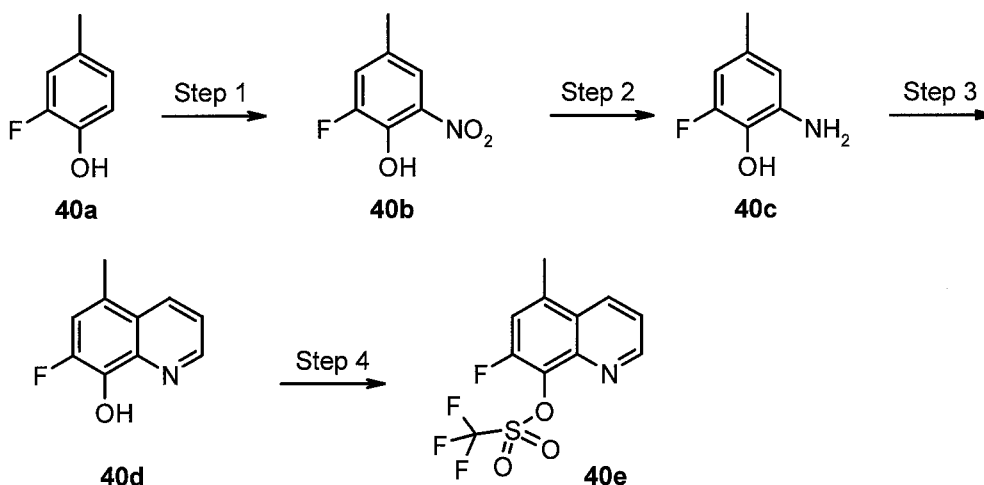
Compound **39i** (600 mg, 3.21 mmol) is taken in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) under nitrogen atmosphere. The solution is cooled to 0°C and triethylamine (0.89 mL, 6.42 mmol) is added dropwise followed by Tf<sub>2</sub>O (0.65 mL, 3.87 mmol). The temperature is raised to RT and the reaction mixture is stirred for 2 h. The mixture is diluted with CH<sub>2</sub>Cl<sub>2</sub> and is washed with H<sub>2</sub>O, brine and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent is removed under reduced pressure to afford a residue which is purified by flash chromatography (10% EtOAc/hexanes). 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, 0.78 mmol), bis(pinacolato)diboron (250 mg, 0.94 mmol), anhydrous potassium acetate (150 mg, 1.51 mmol), Pd(PCy<sub>3</sub>)<sub>2</sub> (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 7 mL of glacial AcOH 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<sub>3</sub>CN/H<sub>2</sub>O gradient containing 0.06% TFA, ODS-AQ, C-18 column, 50 x 19 mm, 5-µm particle size). The collected fractions are lyophilized to give the desired compound **39k** as a yellow amorphous solid (115 mg, 45% yield for the TFA

salt).

**Example 40:** Synthesis of triflate fragment **40e** (used in Example 47)



Step 1:

A solution of fuming  $\text{HNO}_3$  (6.0 mL, 142 mmol) and concentrated  $\text{H}_2\text{SO}_4$  (0.2 mL, 3.8 mmol) in chloroform (150 mL) is added to a solution of 2-fluoro-4-methylphenol **40a** (20.0 g, 159 mmol) in chloroform (100 mL). The resulting mixture is stirred for 2 h at RT and is transferred in a separatory funnel. The solution is washed with  $\text{H}_2\text{O}$ , brine, the organic layer is dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent is evaporated under reduced pressure. The reddish crude solid is crystallized from aqueous ethanol to give compound **40b** as a yellowish solid (17 g, 62% yield).

Step 2:

Compound **40b** is transformed to compound **40c** using the procedure of example **36b**.

Step 3:

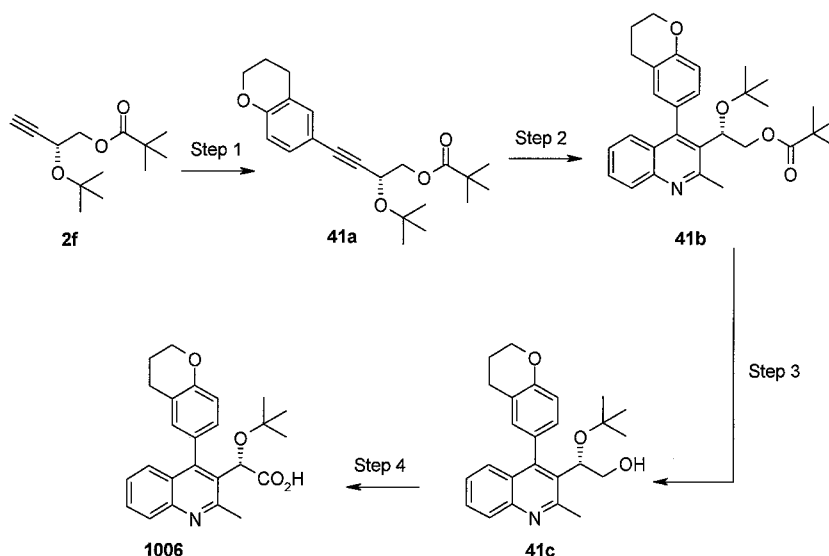
A mixture of concentrated sulfuric acid (12.5 mL, 235 mmol), water (10 mL), glycerol (10.0 mL, 137 mmol) and sodium 3-nitrobenzenesulfonate (9.57 g, 42.5 mmol) is heated gently until everything dissolved. Compound **40c** (5.0 g, 35.5 mmol) is then added slowly to the warm (60°C) solution and the mixture is heated at reflux for 2 h (bath temperature: 140°C). The reaction mixture is then cooled to room temperature and poured into ice-water. The solution is brought to pH 6-7 with an aqueous

ammonia solution. A brown precipitate of compound **40d** formed, it is collected by filtration and dried under high vacuum (5.0 g, 79% yield). This compound is used in the next step without further purification.

#### Step 4:

To a solution of compound **40d** (5.0 g, 28.0 mmol) and triflic anhydride (5.25 mL, 31.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (150 mL) is added dropwise at 0 °C  $\text{Et}_3\text{N}$  (4.7 mL, 33.6 mmol). The resulting mixture is warmed to RT and stirred for 3 h. The reaction mixture is diluted with  $\text{CH}_2\text{Cl}_2$  (50 mL), the solution is washed with 1N HCl, water, brine and it is dried ( $\text{Na}_2\text{SO}_4$ ). The solvent is removed under vacuum to give a dark solid, which is purified by flash chromatography (10% EtOAc / hexanes) to afford the desired compound **40e** as an off-white solid (6.0 g, 68% yield).

#### Example 41: Synthesis of compound 1006



#### Step 1:

Solid  $\text{Pd}(\text{PPh}_3)_4$  (9 mg, 0.008 mmol) and  $\text{CuI}$  (3 mg, 0.015 mmol) are successively added to a solution of **11c** (200 mg, 0.75 mmol) and alkyne **2f** (190 mg, 1.1 mmol) dissolved in DMF (0.46 mL) and diethylamine (2.3 mL). The reaction mixture is stirred overnight at RT and then concentrated, diluted with EtOAc (10 mL) and successively washed with brine, 1 N aqueous HCl and water (10 mL each). The organic layer is dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure and the residue purified by CombiFlash® Companion to give alkyne **41a** (126 mg, 46% yield).

Step 2:

Tf<sub>2</sub>O (96 µL, 0.57 mmol) is added via syringe over the period of 1 min to a stirred mixture of acetanilide (77 mg, 0.57 mmol) and 2-chloropyridine (67 µL 0.71 mmol) in DCM (1.0 mL) at -78 °C. After 5 min, the reaction flask is placed in an ice-water bath and is warmed to 0°C. Alkyne **41a** (102 mg, 0.29 mmol) in DCM (1 mL) is added *via* syringe. The resulting solution is allowed to warm to RT. After stirring for 30 min, Et<sub>3</sub>N (1 mL) is added and the mixture is partitioned between DCM (50 mL) and brine (50 mL). The organic layer is washed with brine (50 mL), is dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue is then purified by CombiFlash® Companion giving quinoline **41b** (81 mg, 60% yield).

Step 3:

LiBH<sub>4</sub> in THF (2 M, 255 µL, 0.51 mmol) is added to a solution of ester **41b** (81 mg, 0.17 mmol) dissolved in THF (900 µL) and the reaction is stirred overnight at RT. Excess reagent is quenched with HCl (three drops, lots of effervescence) and the mixture neutralized with saturated NaHCO<sub>3</sub> (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers are dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give alcohol **41c** (38 mg, 57% yield).

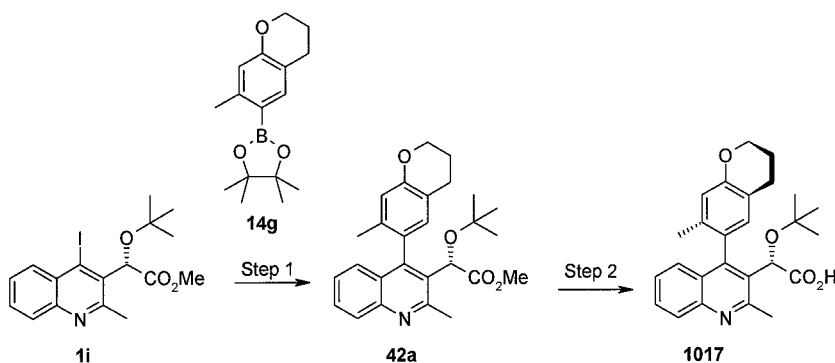
Step 4:

Dess-Martin periodinane (46 mg, 0.11 mmol) is added to a solution of alcohol **41c** (33 mg, 0.084 mmol) dissolved in DCM (1 mL). After 2 h, the reaction is applied to a pad of SiO<sub>2</sub> (1.5 x 1 cm) and the product is eluted with 1:1 hexanes/EtOAc (20 mL). The filtrate is evaporated to give the crude aldehyde. The aldehyde is then dissolved in 2:2:1 THF/H<sub>2</sub>O/t-butanol (2.5 mL) and one drop of 2,3-dimethyl-2-butene (0.8 mL, 1 M in THF) is added. NaClO<sub>2</sub> (62 mg, 0.68 mmol) and NaH<sub>2</sub>PO<sub>4</sub> (51 mg, 0.42 mmol) are added as solids to the solution and the reaction is stirred at RT. After 30 min, the reaction is diluted with H<sub>2</sub>O (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layer is dried over anhydrous MgSO<sub>4</sub> and concentrated. The residue is purified by preparative HPLC to give compound **1006** (12 mg, 27% yield).

It would be apparent to those skilled in the art that the above synthetic protocols can also be used in the synthesis of other inhibitors where either **11c** is replaced by another aromatic halide in Step 1 and/or the acetanilide is replaced with another aryl-

NH-CO-R<sup>2</sup>, or heteroaryl-NH-CO-R<sup>2</sup> (R<sup>2</sup> = CH<sub>3</sub>) in Step 2.

**Example 42: Synthesis of compound 1017**



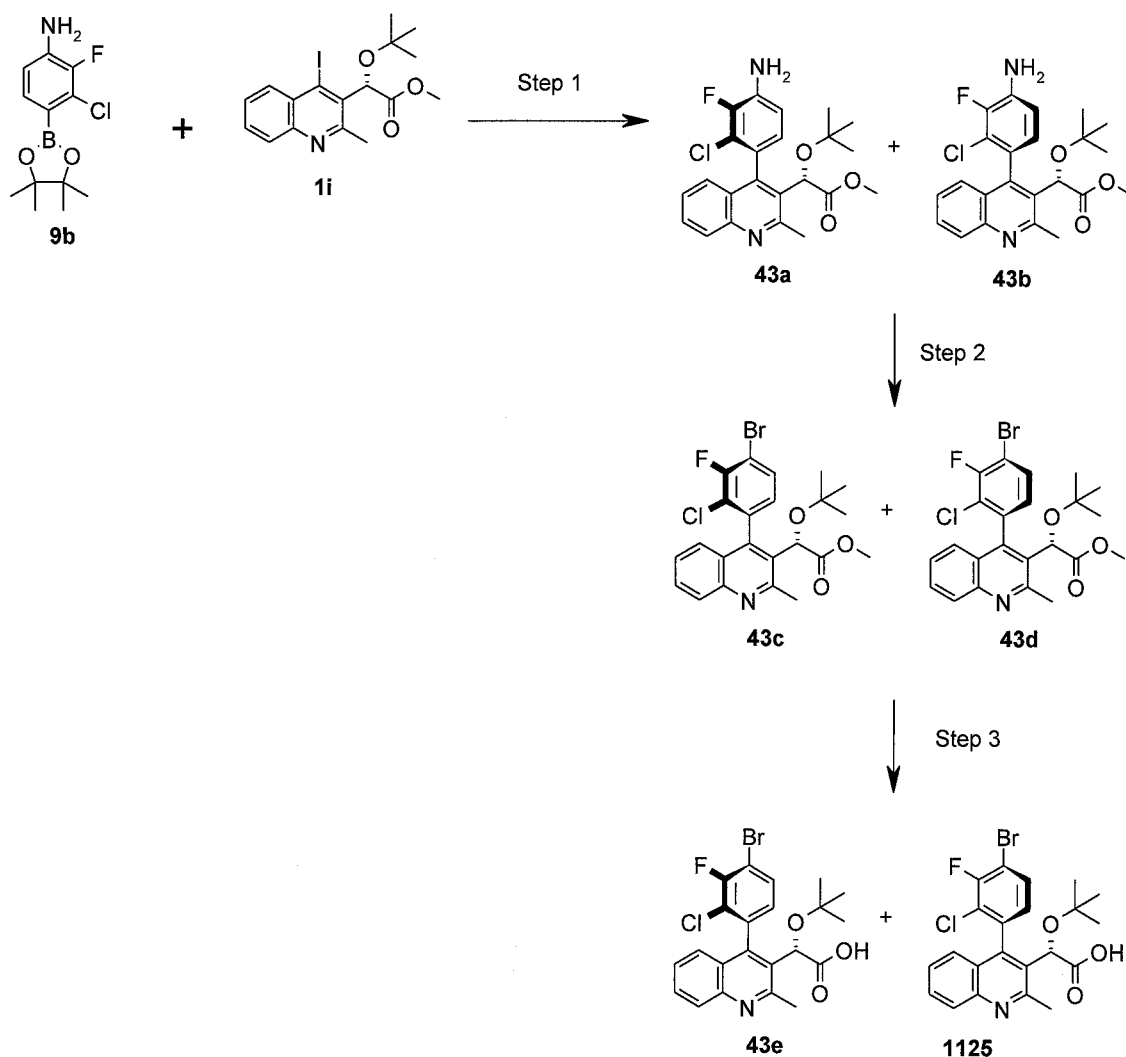
Step 1:

Quinoline **1i** (260 mg, 0.62 mmol), boronic ester **14g** (350 mg, 1.3 mmol) and Pd[P(t-Bu)<sub>3</sub>]<sub>2</sub> (50 mg, 0.098 mmol) are dissolved in DMF (4.3 mL) in a microwave vial and a solution of Na<sub>2</sub>CO<sub>3</sub> (1.25 mL, 2 M, 2.5 mmol) is added. The solution is degassed (Ar balloon) and the mixture is then submitted to microwave heating at 120°C for 10 min. The crude reaction mixture is diluted with water (15 mL) and the product is extracted with EtOAc (15 mL). The organic layer is washed with water (2 x 15 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product is then purified by CombiFlash® Companion (gradient of EtOAc in hexanes) to give quinoline **42a** as a mixture of atropisomers (175 mg, 65% yield).

Step 2:

An aqueous solution of LiOH (4 mL, 1N, 4 mmol) is added to a solution of esters **42a** in THF (25 mL), MeOH (6 mL) and water (12 mL) at RT and the reaction is heated to 50°C. After 4 h, the reaction is evaporated to a white slurry under reduced pressure, diluted with 1 N NaOH (5 mL) and extracted with EtOAc (2 x 25 mL). The water layer is then acidified to pH ~ 3 with 10% HCl and extracted with DCM (2 x 100 mL) and EtOAc (100 mL). The combined organic layers are dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The desired product is isolated after purification of this crude by preparative HPLC to give the desired pure atropisomer (diastereomer) **1017** (7.5 mg, 4.4% yield).

**Example 43: Synthesis of compound 1125**



#### Step 1:

In two separate batches, DMF (15 mL) and distilled water (3.0 mL) are added to two microwave vials each charged with boronate **9b** (560 mg, 2.06 mmol), iodoquinoline **1i** (600 mg, 1.45 mmol), potassium carbonate (602 mg, 4.35 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (252 mg, 0.218 mmol). The vials are then sealed and heated in a microwave reactor (7 min, 140°C). The resulting mixtures are cooled, pooled and extracted with EtOAc (200 mL) and washed with half-saturated aqueous  $\text{NaHCO}_3$  (200 mL) and brine (200 mL). The extract is dried over  $\text{MgSO}_4$ , filtered and evaporated to a red syrup which is chromatographed over silica gel (EtOAc/hexanes) to afford the pure atropisomers **43a** (160 mg, 13% yield) and **43b** (175 mg, 14% yield) as pale yellow amorphous solids, as well as a sample consisting of a mixture of atropisomers which is set aside

for later separation (275 mg, 22% yield).

Step 2:

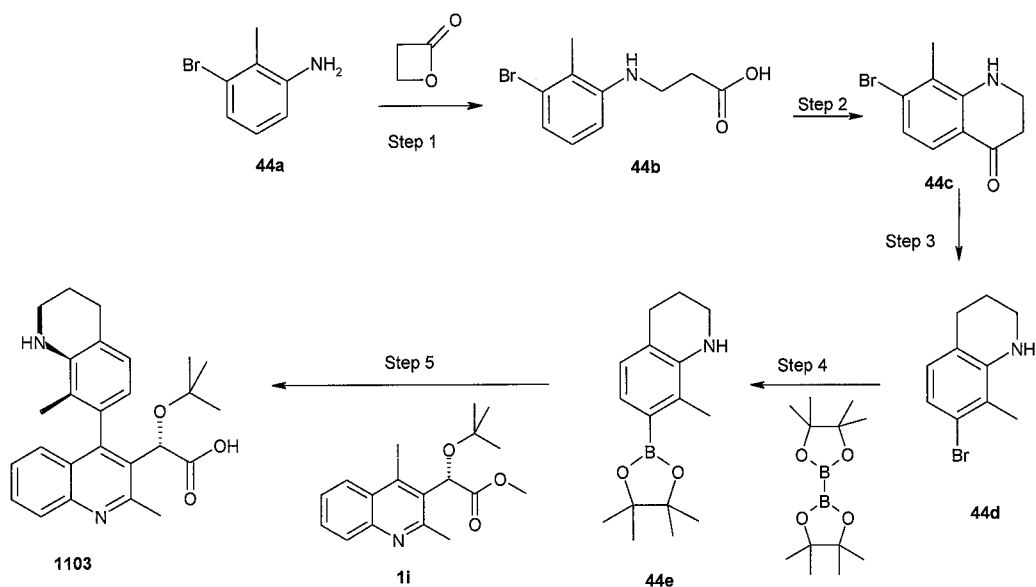
A solution of anilines **43a/43b** (mixture of atropisomers; 50 mg; 0.116 mmol) in anhydrous acetonitrile (0.4 mL) is added to a stirred mixture of copper (II) bromide (32 mg; 0.145 mmol) and tert-butyl nitrite (22  $\mu$ L; 0.19 mmol) in anhydrous acetonitrile (0.6 mL) at RT under an argon atmosphere. After 1 h, the reaction is quenched with 1.0 N HCl and extracted with EtOAc (20 mL) and washed with water (20 mL) and brine (20 mL). The extract is dried over  $\text{MgSO}_4$ , filtered and evaporated to afford a mixture of aryl bromides **43c/43d** as a green solid which is used as such (51 mg; 89% yield).

Step 3:

Sodium hydroxide (1.0 N, 1.00 mL; 1.00 mmol) is added to a stirred solution of the ester mixture **43c** and **43d** (51 mg; 0.103 mmol) in MeOH (1.5 mL) and THF (3 mL) and the reaction heated to 50°C. After 16 h, the solution is acidified with 1.0 N HCl to a pH of ~4 and extracted with DCM (20 mL). The extract is dried over  $\text{MgSO}_4$ , filtered and evaporated to solid which is diluted with acetic acid and acetonitrile (to a volume of 2 mL) and purified by preparative HPLC (0.1 % TFA water / acetonitrile). The relevant fractions are pooled and lyophilized to yield the TFA salts of inhibitors **43e** (13 mg; 27% yield) and **1125** (18 mg; 37% yield) as white powders.

It would be obvious to those skilled in the art that intermediate **43b** could also be used, employing the same methods, to prepare other inhibitors such as the *para*-chloro analogue **1112**. The bromo derivative **43d** could also be transformed via Suzuki coupling to *para*-alkyl derivatives such as **1127**.

**Example 44:** Synthesis of compound **1103**

**Step 1:**

To a solution of 3-bromo-2-methylaniline **44a** (0.77 g, 4.15 mmol) in MeCN (20 mL) is added  $\beta$ -propiolactone (435  $\mu$ L, 6.2 mmol). The reaction mixture is heated at reflux for 16 h. The reaction is found to be incomplete so an equivalent amount of the lactone is added again and the reaction mixture is heated at reflux for 24 h. The solvent is evaporated before the residue is taken up into EtOAc and washed with 1 N HCl (aq) and brine before being dried ( $\text{MgSO}_4$ ), filtered and concentrated. Purification by CombiFlash® Companion (hexanes/EtOAc) gives intermediate **44b** as a white solid (606 mg, 57% yield).

**Step 2:**

Compound **44b** (1.1 g, 4.3 mmol) is combined with polyphosphoric acid (40 g) and heated at 100°C for 22 h. The cooled mixture is diluted with EtOAc and ice before being basified to pH ~ 8 with 10 N NaOH. The phases are separated and the aqueous phase again extracted with EtOAc (3x). The combined organic phases are dried ( $\text{MgSO}_4$ ), filtered and concentrated. Purification by CombiFlash® Companion (hexanes/EtOAc) gives the desired ketone **44c** as a yellow solid (535 mg, 52% yield).

**Step 3:**

To a solution of ketone **44c** (489 mg, 2.04 mmol) in DCE (20 mL) is added zinc iodide (975 mg, 3.06 mmol) and sodium cyanoborohydride (960 mg, 15.3 mmol).

The mixture is heated at 85°C for 1.5 h. The mixture is cooled to RT and diluted with EtOAc and a saturated solution of NH<sub>4</sub>Cl (containing 10% by volume of 6 N HCl). The mixture is stirred for 30 min before the phases are separated. The organic phase is washed with saturated brine and then dried (MgSO<sub>4</sub>) filtered and concentrated. Pure intermediate **44d** (232 mg, 50% yield) is isolated after purification of the crude by CombiFlash® Companion (hexanes/EtOAc).

Step 4:

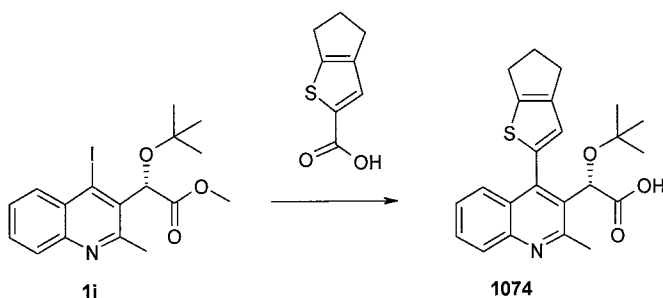
To compound **44d** (260 mg, 1.15 mmol) in anhydrous DMF (10 mL) is added bis(pinacolato)borane (380 mg, 1.5 mmol) followed by potassium acetate (339 mg, 3.45 mmol). The mixture is degassed with Ar for 10 min before the catalyst PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> complex (141 mg, 0.17 mmol) is added. The mixture is heated at 95°C for 20 h before being cooled and diluted with EtOAc and water. The organic phase is washed with saturated brine (3x) before being dried (MgSO<sub>4</sub>), filtered and concentrated. The crude material is purified by CombiFlash® Companion (hexanes/EtOAc) to give the boronate **44e** as a yellow solid (252 mg, 80% yield).

Step 5:

In a vessel suitable for microwave heating, quinoline **1i** (62 mg, 0.15 mmol), boronate **44e** (50 mg, 0.18 mmol), potassium carbonate (62 mg, 0.45 mmol) and Pd[(PPh<sub>3</sub>)<sub>4</sub>] (26 mg, 0.023 mmol) in DMF (2.5 mL) and water (0.25 mL) are added. The mixture is irradiated at 110°C for 15 min in a microwave before being cooled and diluted with EtOAc. The organic phase is washed with brine (3x) before being dried (MgSO<sub>4</sub>), filtered, concentrated and purified by combiflash (hexanes/EtOAc) to obtain a mixture of atropisomers (diastereomers) as a yellow oil. This material (68 mg, 0.16 mmol) is dissolved in THF (1.5 mL) and MeOH (0.5 mL) before being treated with 5 N NaOH (0.32 mL, 1.57 mmol, 10 eq). The mixture is heated at 50°C for 18 h before being cooled. The pH is adjusted to ~5 with aqueous 1 N HCl and the mixture is extracted with EtOAc. The organic phase is washed with saturated brine before being dried (MgSO<sub>4</sub>), filtered and concentrated. The atropisomers (diastereomers) are separated by preparative HPLC to give the desired compound **1103** as a light orange solid (16.8 mg, 20% yield over two steps).

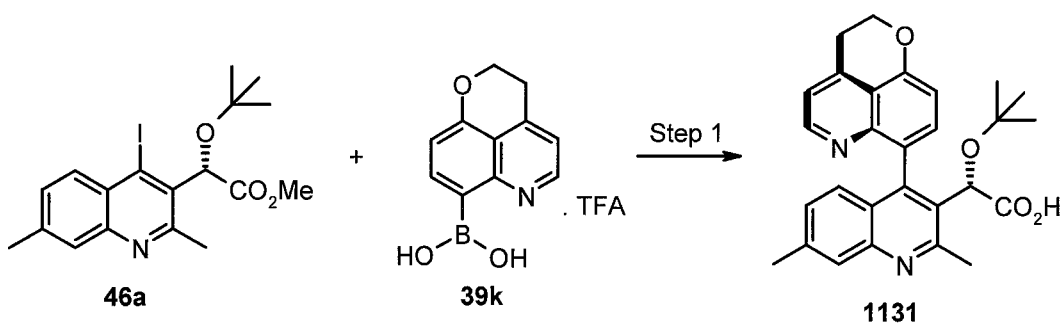
**Example 45:** Synthesis of a compound **1074** via decarboxylative biaryl cross coupling reactions

The decarboxylative cross coupling reactions are used to prepare a variety of inhibitors; the details of the synthetic methodology can be found in the literature reference: *J. Am. Chem. Soc.* **2006**, 128, 11350-11351. An example is shown below:



In a vial suitable for microwave reactions is added 5,6-dihydro-4H-cyclopenta[b]thiophene-2-carboxylic acid (73 mg, 0.44 mmol), 4-iodoquinoline **1i** (100 mg, 0.24 mmol), tetrabutylammonium chloride hydrate (67 mg, 0.24 mmol), cesium carbonate (118 mg, 0.36 mmol), and the catalyst  $\text{Pd}[(\text{PtBu})_3]_2$  (12.4 mg, 0.02 mmol) in DMF (3 mL). The vial is then capped and submitted directly to the microwave conditions: 170°C for 8 min. After cooling, the reaction is diluted with EtOAc (100 mL) and the mixture is washed with brine (3x), water (1x), before being dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue is purified by CombiFlash® Companion (hexanes/EtOAc) to afford the methyl ester of the desired product (79 mg, 80% yield) as a foamy solid. The final compound **1074** is obtained after a saponification step followed by HPLC purification.

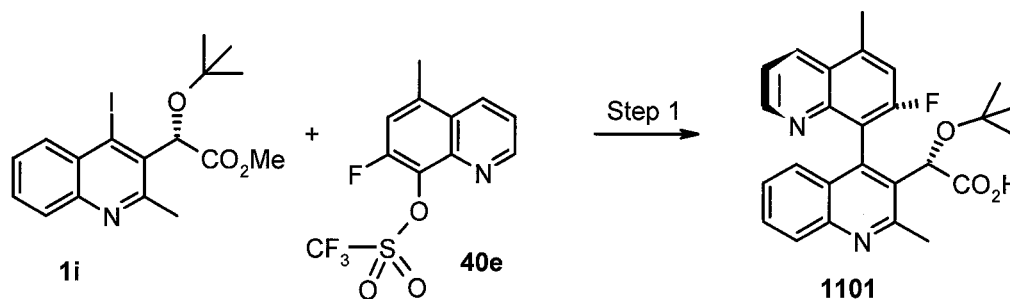
#### Example 46: Synthesis of compound **1131**



In a 5-mL glass microwave vessel containing a magnetic stirring bar, are added

compound **46a** (100 mg, 0.234 mmol), compound **39k** (90 mg, 0.273 mmol), anhydrous potassium carbonate (150 mg, 1.08 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (40.0 mg, 0.035 mmol), anhydrous, deoxygenated (Argon bubbling for 30 min) dimethylacetamide (3 mL) and deoxygenated H<sub>2</sub>O (0.35 mL). The vial is capped and is heated in a microwave at 100°C for 25 min (Biotage Initiator apparatus). The mixture is cooled and THF (3 mL), H<sub>2</sub>O (1 mL), and MeOH (3 mL) are added followed by a 10 N aqueous solution of NaOH (0.50 mL, 5.0 mmol). The reaction mixture is heated to 60°C 1 h. The reaction is cooled and the volatiles are removed under vacuum to give a brown oily residue which is diluted with 7 mL of acetic acid, filtered on a 45 µm membrane filter and injected in 1.5-mL batches into a preparative reversed-phase HPLC-MS for purification (CH<sub>3</sub>CN/H<sub>2</sub>O gradient containing 0.06% TFA, ODS-AQ, C-18 column, 50 x 19 mm, 5-µm particle size). The desired atropisomer is re-purified under the same conditions as described above. **1131** as a white amorphous solid (52.0 mg, 32% yield, bis-TFA salt).

**Example 47: Synthesis of compound 1101**



In a dry pressure tube, compound **1i** (100 mg, 0.24 mmol) is dissolved in anhydrous, deoxygenated THF (2.5 mL, Ar bubbling for 30 min) and the mixture is cooled to -40 °C under Ar atmosphere. A freshly titrated solution of *i*-PrMgCl-LiCl complex in THF (the titration is done following the protocol in Lin, H.S.; Paquette, L. A. Synth. Commun. **1994**, 24, 2503; 0.83 M solution, 0.400 mL, 0.328 mmol, ) is added and is stirred at -40 °C for 30 min.

In a separate flask, a 0.65M solution of zinc chloride in THF is prepared in the following manner: 115 mg (0.84 mmole) of anhydrous zinc chloride is placed in an oven-dried 2 mL glass microwave vessel and is dried at 180°C (oil bath) under high vacuum overnight. The vessel is cooled to room temperature and 1.3 mL of

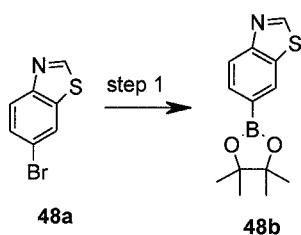
anhydrous, argon-degassed THF is added. The mixture is sonicated until all the zinc chloride dissolved.

The 0.65M solution of zinc chloride in THF (0.50 mL, 0.30 mmol), is added to the reaction mixture at -40°C. It is stirred at this temperature for 5 min and is warmed to -5°C and kept at this temperature for 1 h and finally at RT for an extra hour.

Pd<sub>2</sub>(dba)<sub>3</sub> (24.0 mg, 0.0262 mmol) and RuPhos (24.0 mg, 0.051 mmol, Strem Chemicals) are added under an Ar atmosphere and the mixture is stirred at RT for 5 min. Compound **40e** (80.0 mg, 0.259 mmol) is then added, the reaction vessel is purged with Ar, sealed and heated on an oil bath set at 80°C for 40 h.

The reaction mixture is cooled down and H<sub>2</sub>O (0.30 mL), MeOH (0.30 mL) and 10 N aqueous NaOH (0.30 mL, 3.0 mmol) are added sequentially and the mixture is heated to 60°C for 2 h. Acetic acid is then added (2 mL), the mixture is filtered over a 45 µm membrane filter and the compound is purified in two portions through direct injection into a semi-preparative reversed-phase HPLC-MS (CH<sub>3</sub>CN/H<sub>2</sub>O gradient containing 0.06% TFA, ODS-AQ, C-18 column, 75 x 30 mm, 5-µm particle size). A mixture of two atropisomers is isolated (20 mg, 13% yield for bis-TFA salt). Both atropisomers are separated using silica-gel chromatography (CombiFlash® Companion apparatus, 4 g column, MeOH-CH<sub>2</sub>Cl<sub>2</sub> gradient) to give compound **1101** (5.5 mg, 5% yield) as a pure atropisomer.

**Example 48: Synthesis of boronate fragment 48b (used for the preparation of 1136)**

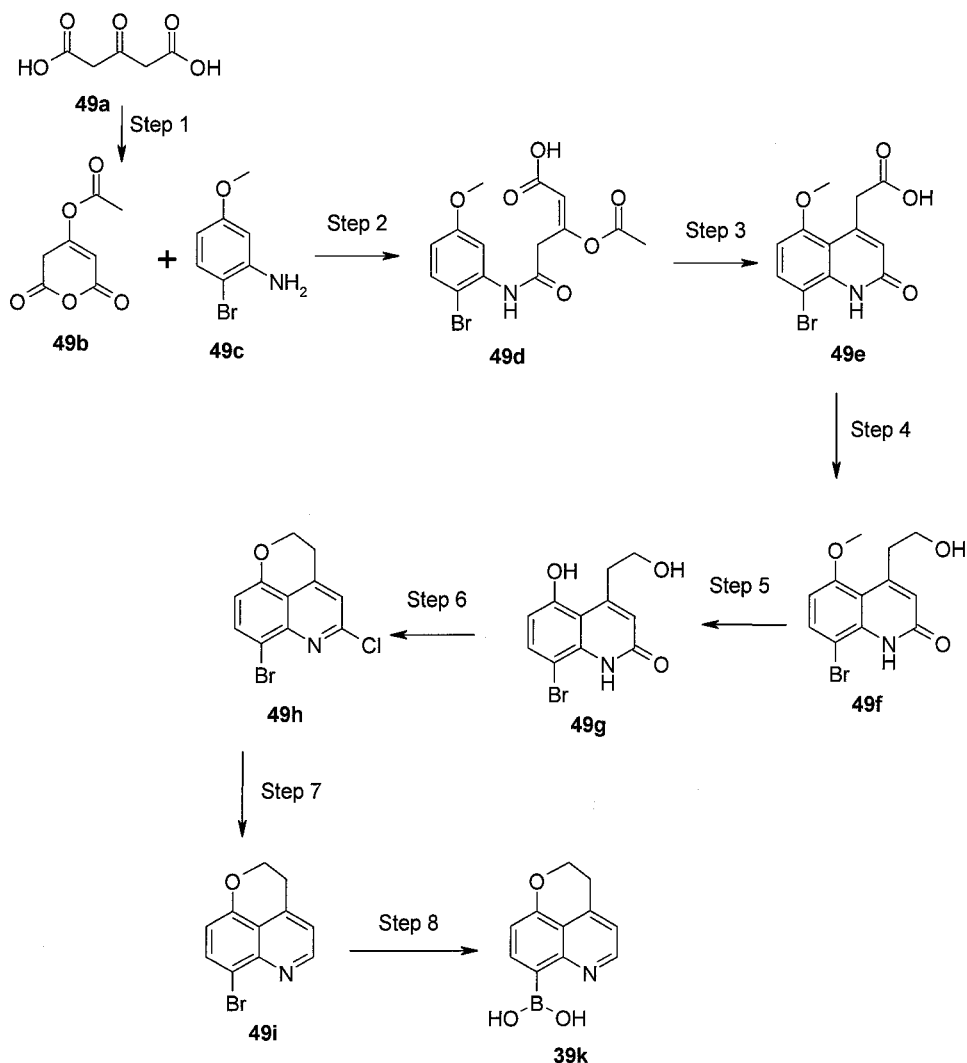


**Step 1:**

A stirred DMF (5 mL) solution of the arylbromide **48a** (0.152 g, 0.71 mmol), potassium acetate (0.209 g, 2.1 mmol) and bis(pinacolato)diborane (0.234 g, 0.92 mmol) is degassed by bubbling Ar through the solution for 20 min. PdCl<sub>2</sub>(dppf)-DCM (87 mg, 0.11 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 16 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<sub>4</sub>, filtered and concentrated to dryness. The residue is purified by CombiFlash® Companion

(EtOAc/hexanes) to give the desired boronate **48b** (144 mg, 77% yield) as a yellowish solid.

**Example 49:** Alternative Synthesis of boronate fragment **39K** (used for the preparation of **1143**, **1144**, **1150**, **1151**, **1152**, **1153**)



**Step 1:**

1,3-acetonedicarboxylic acid **49a** (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 precipitate that formed is filtered and dried under vacuum to give compound **49b** as a pale yellow solid (26.9 g, 70% yield).

Step 2:

To a stirred solution of aniline **49c** (7.5 g, 44 mmol) in AcOH (50 mL) is added **49b** (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 room temperature 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 **49d** (9.1 g, 61% yield).

Step 3:

Compound **49d** (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 **49e** (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 **49e** (1.5 g, 4.8 mmol) in dry THF (40 mL) under a N<sub>2</sub> 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<sub>3</sub> is added at 0°C and the reaction mixture is heated to 45°C for 2 h. The reaction mixture is carefully quenched with 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 **49f** is filtered and dried under vacuum (1.1 g, 79% yield) as grey solid.

Step 5:

To a solution of **49f** (1.1 g, 3.8 mmol) in DCM (60 mL) at -78°C is added dropwise a 1.0 M BBr<sub>3</sub> 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 **49h** 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 **49g** (773 mg, 71% yield).

Step 6:

To a solution of compound **49g** (773 mg, 2.27 mmol) in THF (30 mL) is added PPh<sub>3</sub> (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  $\text{POCl}_3$  (2 mL) at RT. The reaction mixture is stirred at  $100^\circ\text{C}$  for 45 min and then cooled to RT. The mixture is concentrated under vacuum (to remove  $\text{POCl}_3$ ) and the crude product is diluted with DCM. The organic phase is washed with 1.0 N NaOH, water, and brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated under vacuum. The crude product is purified in two batches by combi-flash (330 column hexanes/EtOAc 9/1 to 1/1) to give **49h** as a pale yellow solid (445 mg, 91% yield).

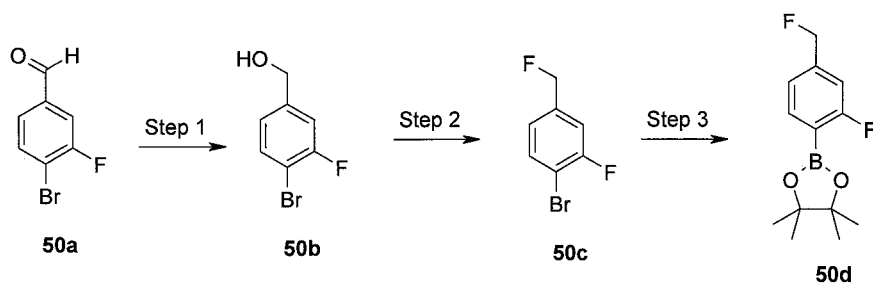
#### Step 7:

To a solution of chloroquinoline **49h** (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 ( $\text{MgSO}_4$ ), filtered and concentrated under vacuum. The crude product was purified by combi flash (hexanes/EtOAc 6/4 to 4/6) to give **49i** as a pale yellow solid (26 mg, quantitative yield).

#### Step 8:

The reaction is done following a procedure similar to the one in step9 of example 39 using  $\text{Pd}(\text{PPh}_3)_4$  as catalyst and starting with **49i** to give **39k** as a white solid.

#### Example 50: Synthesis of boronate fragment **50d** (used for the preparation of **1018**, **1020**)



#### Step 1:

Solid  $\text{NaBH}_4$  (603 mg, 15.9 mmol) is added to a solution of ketone **50a** (4.11 g, 19.92 mmol) dissolved in MeOH (62 mL) at  $0^\circ\text{C}$ . The reaction is warmed to RT and is allowed to stir for 2 h. The reaction is quenched with aqueous HCl (1 N, 20 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  $\text{MgSO}_4$ , filtered and concentrated to afford alcohol **50b** (4.1 g, 97% yield). This material is used as is in the next step.

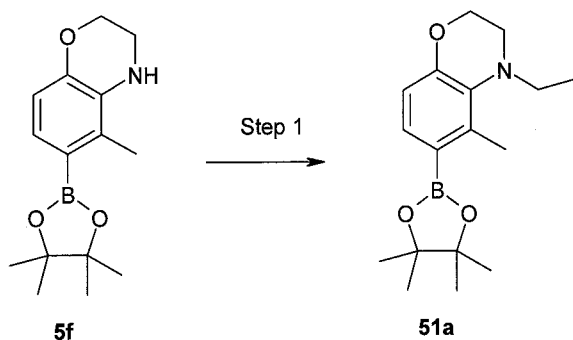
Step 2:

To a cold solution ( $0^\circ\text{C}$ ) of **50b** (3.96 g, 19.31 mmol) in DCM (12 mL) is added diethylamino sulfur trifluoride (2.78 mL, 21.25 mmol). The reaction is warmed to RT and is allowed to stir for 2 h. The reaction is quenched with aqueous  $\text{NaHCO}_3$  and extracted with DCM. The organic layer is dried with  $\text{MgSO}_4$ , filtered and evaporated to dryness. The product is purified by CombiFlash® Companion to afford **50c** (2.1 g, 52% yield) as a colorless oil.

Step 3:

Step 3 is carried out exactly as in step 1 of example 48 to provide boronic ester **50d**.

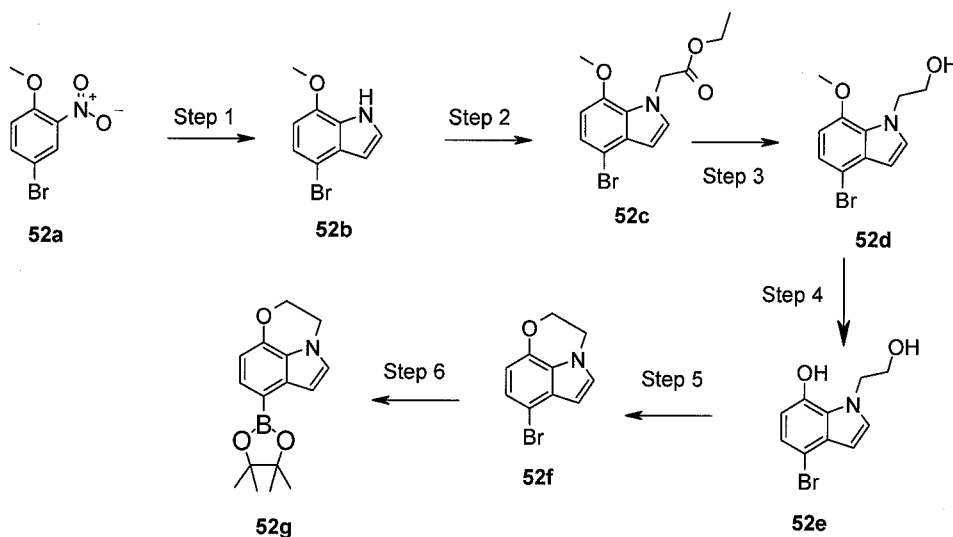
**Example 51:** Synthesis of boronate fragment **51a** (used for the preparation of **1115**)



Step 1:

To a cooled solution ( $0^\circ\text{C}$ ) of boronate **5f** (400 mg, 1.45 mmol) in anhydrous DMF (8 mL) is added NaH (87.4 mg, 2.18 mmol, 60% dispersion in oil). The mixture is stirred for 30 min before being treated with iodoethane (233  $\mu\text{L}$ , 2.9 mmol). The resultant mixture is stirred for 18 h before being quenched with water and extracted with EtOAc. The organic phase is washed with brine and dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue is purified by CombiFlash® Companion (EtOAc/hexanes) to give **51a** as colourless oil (317 mg, 72%).

**Example 52:** Synthesis of boronate fragment **52g** (used for the preparation of **1149**)

**Step 1:**

To a solution of 4-bromo-1-methoxy-2-nitro-benzene **52a** (6 g, 25.9 mmol) in dry THF (250 mL) at  $-40^{\circ}\text{C}$  is added dropwise the vinylmagnesium bromide solution (1M in THF, 90.5 mL, 90.5 mmol). The reaction mixture is stirred at  $-40^{\circ}\text{C}$  for 4 h then poured into saturated  $\text{NH}_4\text{Cl}$  solution. The reaction mixture is extracted with  $\text{Et}_2\text{O}$  (2x); the combined organic layers are washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting  $\text{EtOAc}$ /hexanes (10% to 40%) affording **52b** (620 mg, 11% yield).

**Step 2:**

A solution of indole **52b** (619 mg, 2.7 mmol) in DMF (5 mL) at  $23^{\circ}\text{C}$  is treated with NaH (60% in oil dispersion, 125 mg, 5.2 mmol) and stirred at  $23^{\circ}\text{C}$  for 5 min. Ethyl bromoacetate (637  $\mu\text{L}$ , 5.75 mmol) is added and the solution is stirred at  $23^{\circ}\text{C}$  for 24 h; UPLC/MS analysis indicated 62 % conversion. To this mixture, additional amounts of NaH (60% in oil dispersion, 77 mg, 1.9 mmol) and ethyl bromoacetate (244  $\mu\text{L}$ , 2.2 mmol) are added. After 10 min, the UPLC analysis indicated > 90% conversion. The reaction is diluted with  $\text{EtOAc}$ , washed with saturated  $\text{NH}_4\text{Cl}$  solution and brine (4X), dried over  $\text{MgSO}_4$ , filtrated, concentrated and purified by flash chromatography (5-20 %;  $\text{EtOAc}$ /hexanes) to give **52c** (541 mg, 63 % yield) as a yellow oil.

**Step 3:**

To a solution of **52c** (385 mg, 1.2 mmol) in THF (12.3 mL) is added  $\text{LiBH}_4$  solution (2 M in THF, 1.54 mL, 3.1 mmol). The mixture is stirred at RT for 16 h, then cooled to  $0^{\circ}\text{C}$

and neutralized with  $\text{NH}_4\text{Cl}$  (sat). The resulting solution is extracted with ethyl acetate (2 x) and combined organic layers are washed with water, brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* providing the compound **52d** (317 mg, 95% yield).

Step 4:

To a solution of **52d** (284 mg, 1.05 mmol) in DCM (9.7 mL) at RT is added the  $\text{AlCl}_3$  (561 mg, 4.2 mmol). This mixture is stirred at RT for 16h, then cooled to  $0^\circ\text{C}$  and methanol is added. The resulting solution is concentrated *in vacuo*. The residue is diluted with DCM containing 5% MeOH and a mixture of brine/ water 50:50. The resulting solution is extracted with DCM until no more products remained in the aqueous layer. The organic layer is dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. Purification by flash chromatography (2-10%, methanol/DCM) gives the compound **52e** (200 mg, 74% yield).

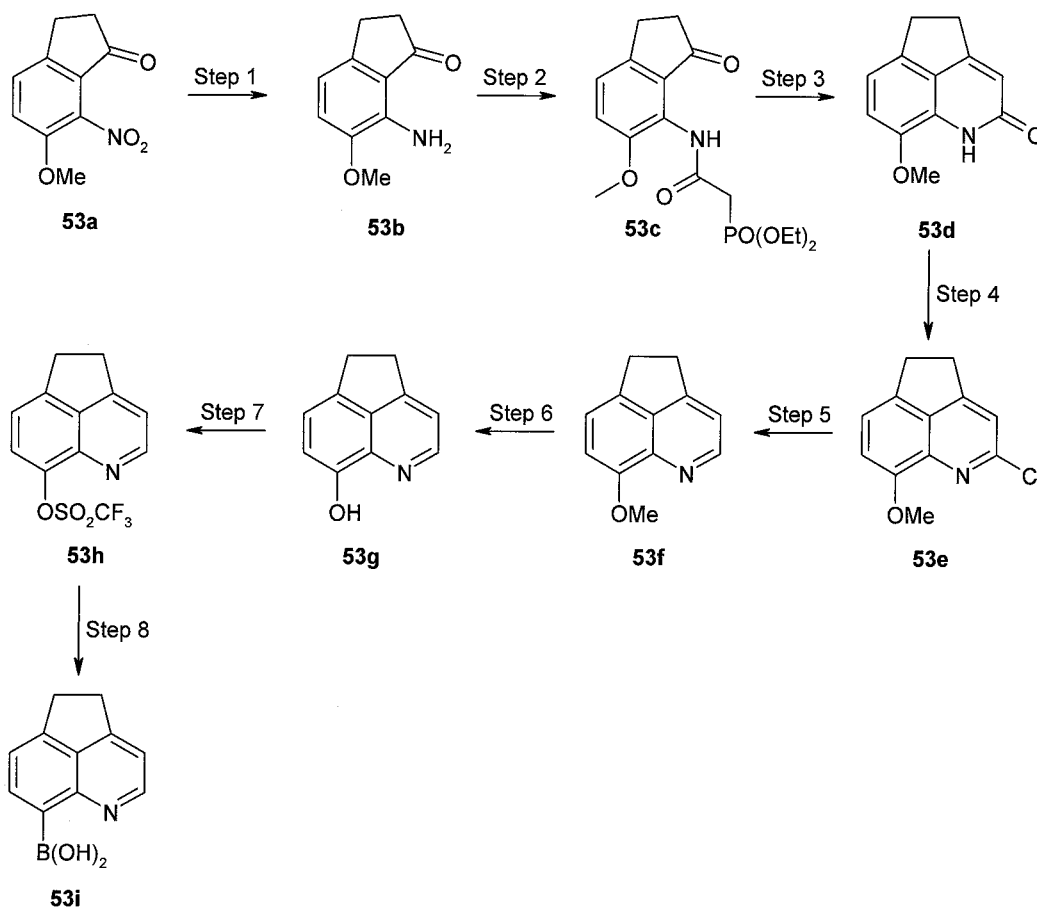
Step 5:

To a solution of **52e** (170 mg, 0.66 mmol) in DCM (10 mL) at  $0^\circ\text{C}$  is added the triethylamine (204  $\mu\text{L}$ , 1.46 mmol). Methanesulfonyl chloride (62  $\mu\text{L}$ , 0.8 mmol) is added and the mixture is stirred at  $0^\circ\text{C}$  for 10 min. The reaction is not completed, additional methanesulfonyl chloride (30  $\mu\text{L}$ , 0.4 mmol) is added and the mixture is stirred at  $0^\circ\text{C}$  for 10 min. Poured into ice water the extracted with  $\text{CH}_3\text{Cl}$  (3x). Combined organic layers are washed with saturated  $\text{NH}_4\text{Cl}$ ,  $\text{NaHCO}_3$ , brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude intermediate (261 mg, 0.78 mmol) is diluted in DMF (5.3 mL) and NaH (60% in oil dispersion, 52.9 mg, 1.3 mmol) is added at  $0^\circ\text{C}$ . The mixture is stirred at RT for 16 h.  $\text{Et}_2\text{O}$  and brine are added, layers separated and the organic layer is washed with brine (2x), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The product is then purified by flash chromatography eluting EtOAc/hexanes (10 - 25 %) to give **52f** (170 mg, 91% yield).

Step 6:

Step 6 is carried out exactly as in step 1 of example 48 to provide boronic ester **52g**.

**Example 53:** Synthesis of boronate fragment **53i** (used for the preparation of **1141**, **1148**)

**Step 1:**

To a solution of **53a** (10.0 g, 48.3 mmol) in acetic acid (150 mL) at RT is added iron (10.8 g, 193 mmol) and the reaction mixture is stirred at 70°C for 2 h. The cooled reaction mixture is filtered and the filtrate concentrated under vacuum. The residue diluted with EtOAc (300 mL) is washed with water (100 mL), brine (100 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under vacuum to give **53b** as a yellow solid (8.8 g, 100% yield). This material is used in the next step without further purification.

**Step 2:**

To a solution of aniline **53b** (8.8 g, 49.7 mmol) and diethylphosphonoacetic acid (8.8 mL, 54.6 mmol) in DCM (300 mL) is added HATU (22.7 g, 59.6 mmol) followed by DIPEA (21.6 mL, 124 mmol). The reaction mixture is stirred at RT for 3 h. After that period, the transformation is incomplete, therefore, more diethylphosphonoacetic acid (4.0 mL, 24.9 mmol), HATU (9.4 g, 24.9 mmol) and DIPEA (4.3 mL, 24.9 mmol) are added. The mixture is stirred for another 2 h. The mixture is diluted with DCM (300 mL), washed with aqueous 0.2N HCl (3 x 100 mL), aqueous 0.2N NaOH (3 x 100 mL), water (100 mL) and brine (100 mL). The organic phase is dried over

MgSO<sub>4</sub>, filtered and concentrated under vacuum. The residue is dried under vacuum overnight to give the desired product **53c** as a pale orange solid (16.0 g, 60% yield). This material is used in the next step without further purification.

Step 3:

To a solution of **53c** (16.0 g, 26.9 mmol) in THF (180 mL) at 50°C is carefully added NaH (60% in oil, 1.2 g, 29.6 mmol) and the reaction mixture is stirred for 2 h. The cooled reaction mixture is quenched with MeOH (20 mL) and silica gel (50 g) is added. The mixture is concentrated under vacuum and purified by CombiFlash® Companion (DCM/MeOH) to give the desired intermediate **53d** (1.8 g, 27% yield).

Step 4:

A solution of **53d** (1.8 g, 7.1 mmol) in POCl<sub>3</sub> (30 mL, 322 mmol) is stirred at 110°C for 45 min. The cooled reaction mixture is concentrated under vacuum. The residue is diluted with DCM (100 mL), washed with aqueous 1.0N NaOH (50 mL), water (50 mL), and brine (50 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The crude product is purified by CombiFlash® Companion (DCM/MeOH) to give the desired chloroquinoline **53e** (1.3 g, 81% yield).

Step 5:

A solution of **53e** (1.3 g, 5.8 mmol) in EtOH (100 mL) is degassed by bubbling argon for 45 min. Palladium (10 wt. % on activated carbon, 1.0 g) is added to the solution and the reaction mixture is stirred under an atmospheric pressure of hydrogen for 6 h. The reaction mixture is filtered and the filtrate concentrated under vacuum to give **53f** (1.1 g, 100% yield). This material is used in the next step without further purification.

Step 6:

To a solution of **53f** (1.1 g, 5.8 mmol) in DCM (40 mL) at 0°C is added a BBr<sub>3</sub> solution (1M in heptane, 12.7 mL, 12.7 mmol). The reaction mixture is stirred for 30 min at 0°C and then slowly allowed to warm to Rt and stirred at this temperature for 24 h. The reaction mixture is quenched with MeOH (10 mL) and neutralized with aqueous 1.0 N NaOH. The yellow precipitate that formed is filtered and dried under vacuum to give the desired product **53g** (984 mg, 100% yield). This material is used in the next step without further purification.

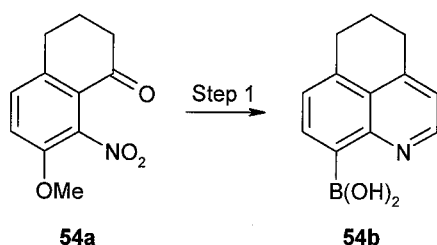
Step 7:

To a solution of **53g** (984 mg, 5.7 mmol) and Et<sub>3</sub>N (4.0 mL, 28.7 mmol) in DCM (40 mL) cooled to -78°C is added Tf<sub>2</sub>O (2.1 mL, 12.6 mmol). The resulting dark solution is stirred for 15 min at -78°C and then slowly allowed to warm to RT and then stirred at this temperature for 3 h. The reaction mixture is diluted with DCM (50 mL), washed with aqueous 0.2 N HCl (25 mL), aqueous saturated NaHCO<sub>3</sub> (25 mL), water (25 mL), brine (25 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The residue is purified by CombiFlash® Companion (DCM/MeOH) to give triflate **53h** (755 mg, 43% yield).

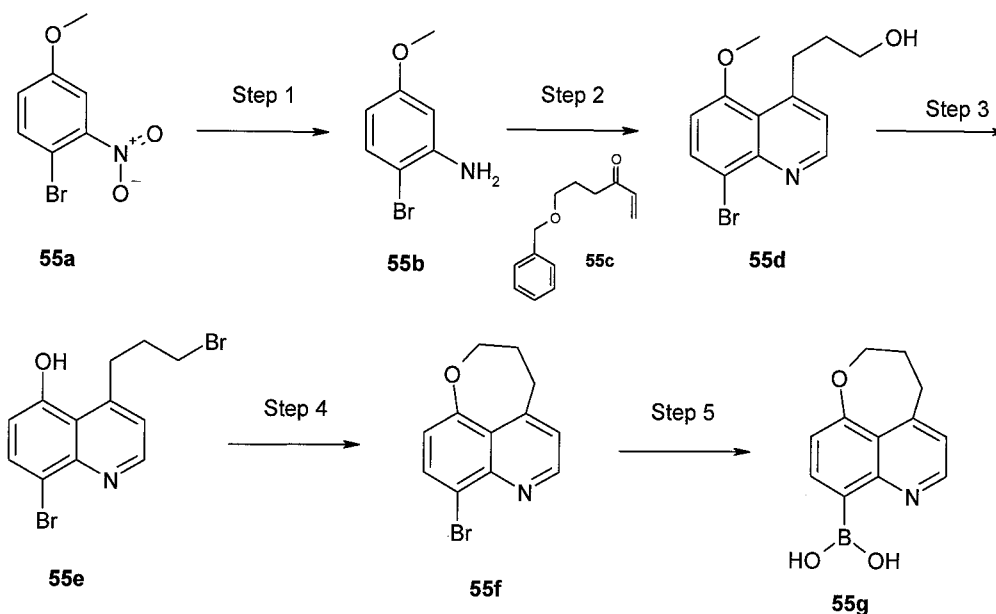
Step 8:

A well stirred DMF (7 mL) solution of triflate **53h** (555 mg, 1.8 mmol), potassium acetate (608 mg, 6.4 mmol) and bis(pinacolato)diborane (697 mg, 2.7 mmol) is degassed by bubbling argon through the solution for 20 min. PdCl<sub>2</sub>(dppf)-DCM (224 mg, 0.27 mmol) is added and degassing is continued for 15 min. The system is sealed (Teflon screw cap vessel) under argon and heated to 95°C for 7 h. The mixture is poured in aqueous 1N HCl (30 mL) and diluted with EtOAc (15 mL). The layers are separated and the aqueous layer is neutralized to pH 7 with aqueous 1.0 N NaOH. This neutral aqueous layer is extracted with EtOAc (3 x 25 mL). The combined organic extracts are washed with brine (25 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The boronic acid **53i** (290 mg, 80% yield) is used as such for the following step.

**Example 54:** Synthesis of boronate fragment **54b** (used for the preparation of **1145**)

Step 1:

Compound **54b** is prepared from **54a** following a synthetic sequence identical to steps 1 to 8 of Example 53.

**Example 55:** Synthesis of boronate fragment **55g** (used for the preparation of **1147**)Step 1:

To a 1L flask equipped with a mechanical stirrer is added **55a** (30 g, 129 mmol) in acetic acid (300 mL). To this mixture is added iron powder (14.4 g, 258 mmol) slowly in aliquots. The mixture is heated at 50°C for 2 h before an additional 7.2 g (129 mmol) of iron powder is slowly added. After 1.5 h at 50°C, the conversion to the aniline is complete. The solution is cooled to RT and diluted with 500 mL of EtOAc before being filtered through Celite. The filtrate is concentrated and the crude product is partitioned between EtOAc (1L) and 200 mL of water. The mixture is vigorously shaken and the organic phase is washed with 200 mL of brine, dried over  $\text{MgSO}_4$ , filtered and concentrated to give aniline **55b** (23.7 g, 91%) as a brown oil which is used directly in the next step.

Step 2:

Aniline **55b** (600 mg, 3 mmol) is treated with 6N HCl (8 mL) and sonicated until a white suspension appears (HCl salt). This mixture is heated to 100°C before being treated with the vinyl ketone **55c** (1.2 g, 5.9 mmol) which is prepared similarly to that reported (Ref: Bull. Korean Chem. Soc. 24 (2003) 1, 13-14) but via the Weinreb amide. The reaction mixture is heated at reflux for 6 h, then stirred at RT for 16 h. The mixture is diluted with EtOAc and basified with 10N NaOH. The organic phase is separated and the aqueous phase re-extracted with EtOAc. The combined organic layers are washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated. The material

is purified by Combiflash® Companion (EtOAc/hexanes) to afford the desired alcohol **55d** (330 mg, 37.5%) as a pale brown solid.

Step 3:

BBr<sub>3</sub> (3.34 mL, 3.34 mmol, 1M solution in DCM) is added to a solution of alcohol **55d** (330 mg, 1.12 mmol) in DCM (10 mL) at RT. The reaction mixture is stirred at RT for 16 h, then is quenched with MeOH and concentrated to dryness. The residue is taken up into DCM and washed with water and brine before being dried (MgSO<sub>4</sub>) filtered and concentrated to afford the bromophenol **55e** (384 mg, 100%). This material is used in the next step.

Step 4:

a mixture of bromophenol bromophenol **55e** (345 mg, 1.14 mmol) and K<sub>2</sub>CO<sub>3</sub> (315 mg, 2.28 mmol) in MeCN (20 mL) is treated at RT for 2 h. The mixture is then concentrated to dryness and the residue dissolved in EtOAc before being washed with water and brine. The organic phase is dried (MgSO<sub>4</sub>), filtered and concentrated before the residue is purified by Combiflash® Companion (EtOAc/hexanes) to afford the cyclic ether **55f** (301 mg, 60%) as an amber solid.

Step 5:

In a screw-cap pressure tube is added the cyclic ether **55f** (180 mg, 0.68 mmol), bispinocolatoborane (260 mg, 1.0 mmol), potassium acetate (226 mg, 2.4 mmol) and Pd(dppf)Cl<sub>2</sub>.DCM complex (83 mg, 0.10 mmol) in dry DMF (4 mL). The resulting mixture is de-gased with Argon (5 min). The tube is sealed and stirred at 95°C for 2.5 h. The mixture is treated with 1N HCl (10 mL) before being diluted with EtOAc. After separation of the layers, the aqueous phase was neutralized with 1N NaOH (using a pH meter) to pH 7.0 and is extracted with EtOAc (3X). The combined organic layers are washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated to afford the boronic acid **55g** (124 mg, 79%). This material is used as is in the final cross coupling reaction.

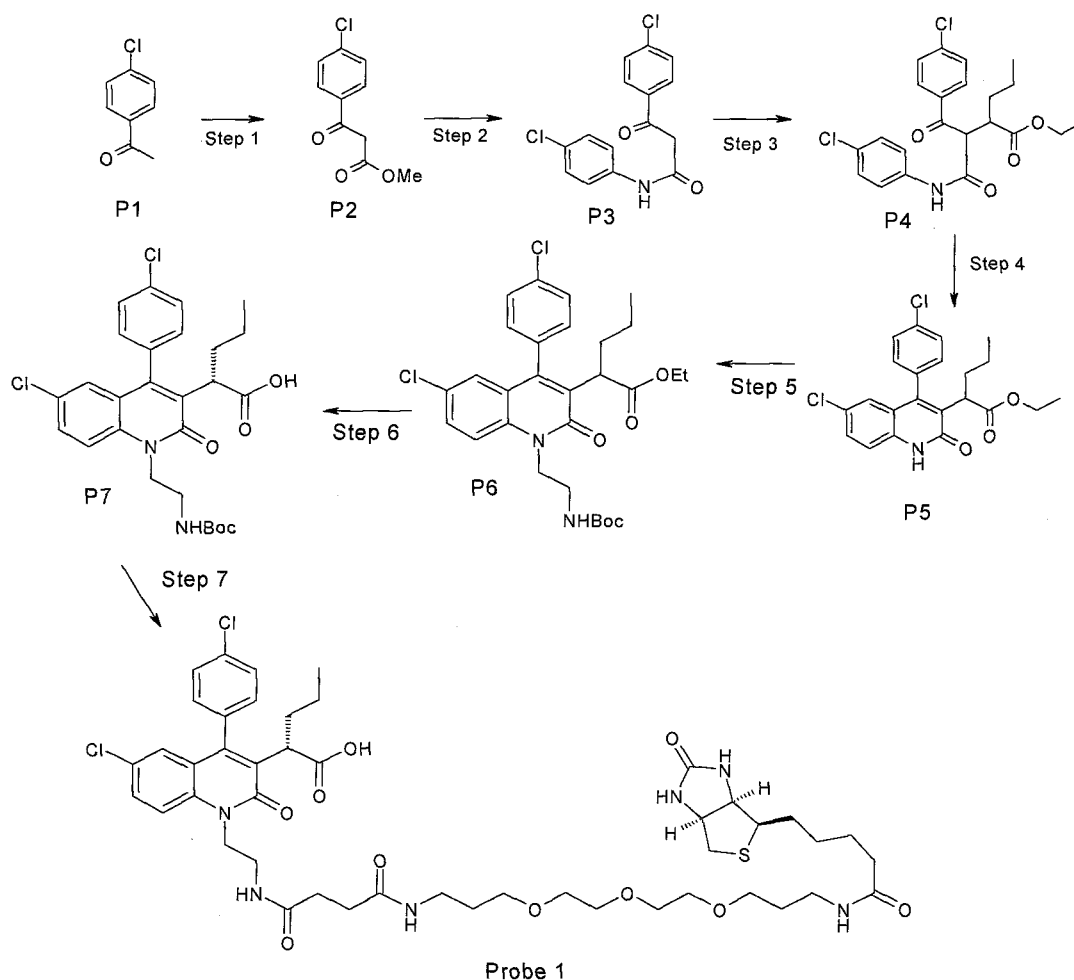
Biological Data

The compounds of the invention have valuable pharmacological properties. Compounds from this class strongly associate with the integrase target as demonstrated by an integrase displacement assay, are particularly effective at

inhibiting HIV integrase and additionally show unexpected potency across at least four or all six major HIV-1 virus HIV variants at residues 124, 125.

**Integrase Displacement Assay** A displacement assay is used to evaluate the relative affinity of compounds of the invention to bind reversibly with HIV integrase. The displacement assay measures the extent to which Probe I (consisting of a HIV integrase inhibitor connected by a flexible linker to a biotin molecule), in complex with a His-tagged HIV integrase, is displaced by compounds of the invention. The integrase-Probe I complex is formed in the presence or absence of inhibitor compounds and the interaction is monitored by a homogeneous time resolved fluorescence (hTRF) assay system.

**Example 56: Production of Probe I:**



**Step 1:**

Dimethyl carbonate (22 mL, 269 mmol) and NaH (60% in oil, 10.8 g, 270 mmol) are combined in toluene (80 mL) and heated to 90°C for 20 min, then

4-chloroacetophenone **P1** (14 mL, 109 mmol) is added dropwise over ca. 15 min. The mixture is stirred at 90°C for 30 min, then cooled and carefully treated with 5% HCl (aq) (100 mL) and EtOAc (100 mL). The organic phase is washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated to dryness. The residue is purified by flash chromatography (15% EtOAc/hexanes) to give compound **P2**.

Step 2:

A mixture of compound **P2** (7.1 g, 33.4 mmol) and 4-chloroaniline (5.9 g, 46.3 mmol) in DMF/xylene (7 mL/40 mL) is heated at 140°C for 10 h. The cooled mixture is partitioned between 1M HCl (40 mL) and EtOAc (150 mL). The organic layer is washed with 1M HCl, water and brine, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness. The residue is purified by flash chromatography (SiO<sub>2</sub>, 15% to 20% EtOAc/hexanes) to give compound **P3**.

Step 3:

To a mixture of compound **P3** (4.79 g; 15.5 mmol), KOtBu (2.0 g; 18.57 mmol) and DMF (23 mL) is added ethyl-2-bromovalerate (3.2 mL, 18.25 mmol). The mixture is allowed to stir at RT for 16 h, then is poured over ice into a solution of 1N HCl (100 mL) and the mixture is extracted with EtOAc (2X100 mL). The combined organic extracts are washed with brine (4X), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to afford, after purification by chromatography (EtOAc/ hexanes) compound **P4** as a mixture of diastereoisomers.

Step 4:

A mixture of compound **P4** (in separate portions of 1.26 g, 0.77 g and 1.09 g; 7.15 mmol total) and H<sub>2</sub>SO<sub>4</sub> (in separate portions of 24 mL, 15 mL and 19 mL) is allowed to react at 150°C for 20 minutes. The combined reaction mixture is allowed to cool slightly and added dropwise to ice-water. The mixture is extracted with EtOAc (3X), washed with brine (1X), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue (0.69 g, 1.76 mmol) is dissolved in EtOH (25 mL) and to this solution is added POCl<sub>3</sub> (2.4 mL; 27 mmol). The reaction is heated at reflux for 1 h, then poured into ice-water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X). The organic phase is washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated and the residue is purified by chromatography to afford compound **P5**.

Step 5:

A solution of (Boc)<sub>2</sub>O (1M in THF, 2.47 mL, 2.47 mmol) is added to a solution of H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>Br·HBr (506 mg, 2.47 mmol) and Et<sub>3</sub>N (860 µL, 6.175 mmol) in THF (10 mL). The reaction mixture is stirred at RT for 18 h and is partitioned between EtOAc (100 mL) and saturated aqueous NaHCO<sub>3</sub> (25 mL). The organic phase is washed with brine, dried over anhydrous MgSO<sub>4</sub> and concentrated. The residue is purified by chromatography (5% to 20% EtOAc/hexanes) to give BocNHCH<sub>2</sub>CH<sub>2</sub>Br.

To a cooled solution (0°C) of compound **P5** (200 mg, 0.495 mmol) in DMF (3 mL) is added KOtBu (67 mg, 0.598 mmol). The mixture is stirred for 15 min, then a solution of BocNHCH<sub>2</sub>CH<sub>2</sub>Br (160 mg, 0.717 mmol) in DMF (2 mL) is added. The reaction mixture is stirred at RT for 18 h. Water (1 mL) is added, the mixture was diluted with EtOAc (100 mL) and the organic phase is washed with saturated aqueous NaHCO<sub>3</sub> (25 mL) and brine, dried over anhydrous MgSO<sub>4</sub> and concentrated. The residue is purified by chromatography (10% to 30% EtOAc/hexanes) to give compound **P6**.

Step 6:

To a solution of compound **P6** (96 mg, 0.175 mmol) in DMSO (2.5 mL) is added 5N NaOH (175 µL, 0.875 mmol). The mixture is stirred for 30 min and purified by semi preparative HPLC to afford the Boc-protected carboxylic acid. The compound is treated with Boc<sub>2</sub>O in the presence of NaOH to provide compound **P7** as a racemic mixture. Separation by chiral HPLC, using a ChiralCel OD-R column (20x250 mm from Chiral Technologies Inc) and an isocratic solvent system of 20% H<sub>2</sub>O (containing 0.06% TFA) and 80% of a solvent mixture composed of 75% MeCN in H<sub>2</sub>O (containing 0.06% TFA) provides the (S)-enantiomer **P7**.

Step 7:

To a mixture of compound **P7** (9.2 mg, 0.017 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) is added TFA (750 µL). The mixture is stirred at RT for 1 h and concentrated. The residue is dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and to this mixture is added Et<sub>3</sub>N (7 µL, 0.051 mmol), followed by EZ-Link™ TFP-PEO-biotin (Pierce; 17.2 mg, 0.025 mmol). The reaction mixture is stirred at RT for 18 h, the solvent is evaporated and the residue is purified by semi-preparative HPLC to afford biotinylated **Probe I**.

Probe I is determined to have a dissociation constant (K<sub>d</sub>) of 1 µM, as measured by Isothermal Titration Calorimetry (ITC) according to known methods, for example as

described in Shaw-Reid et al. *J Biol Chem.* 278(5):2777-80 (2003).

His-tagged HIV integrase: His-tagged integrase is cloned and expressed in a similar manner as outlined in Barsov et al., *J. Virol.*, Vol 70, No. 7, 4484-4494, (1996).

Briefly, the integrase gene is PCR amplified from a plasmid containing the HXB2 provirus using forward and reverse primers that span the first and final codons of integrase, respectively. Primers contain a 5' NdeI (forward primer) and 3' XhoI site (reverse primer) which allows for cloning of the NdeI / XhoI fragment into the Pet28a bacterial expression vector (Novagen). DH5 $\alpha$  E.coli cells are used to generate and propagate the DNA vectors while BL21 pLysS E.coli cells are used for expression of the His-tagged protein.

His-tagged HIV-1 integrase is expressed in BL21 pLysS cells (Stratagene) to an O.D. of 1.4 in a 30 L fermentor at 37 °C and induced with 0.5 mM IPTG for 3 hours at 37 °C. The bacterial pellet is re-suspended in freshly prepared extraction buffer (20 mM NaPi pH 5.8, 1 M NaCl, 1 M urea, 1 mM TCEP, 20 mM imidazole, 1 mM PMSF, and 1.5 mL Sigma protease inhibitor cocktail for 35 mg pellet) and sonicated. The cell lysate is subjected to centrifugation at 100,000 G for 30 min and the supernatant is loaded onto a HiTrap Ni<sup>2+</sup> column. The column is washed with the extraction buffer containing 100 mM imidazole and eluted in a 15 min linear gradient to 1 M imidazole. The His-Integrase fractions are pooled and diluted 1 to 8 in fresh S column buffer (20 mM Na Pi pH 5.8, 1 mM TCEP, 1 mM EDTA, 1 M urea, 10% glycerol) and loaded onto a HiTrap S column. The column is washed with S column buffer then eluted in an 80 min linear gradient from 0 to 1 M NaCl. Protein fractions are run on an SDS-PAGE gel and the most concentrated samples without contaminant bands are pooled and precipitated with 60% ammonium sulfate. The precipitate is then re-suspended in storage buffer (20 mM Hepes pH 7.5, 500 mM NaCl, 10% glycerol, 0.5 mM TCEP) then loaded onto a SD200 gel filtration column. The His-tagged Integrase containing fractions are pooled, dosed for protein concentration and stored at -80 °C in aliquots. The His-tagged integrase samples are thawed on ice and diluted to the desired concentration in assay buffer for use in the integrase displacement assay.

#### Homogenous time resolved fluorescence (HTRF) assay system

The relative binding affinity of compounds of the invention to the HIV integrase target is assessed using a HTRF system based on fluorescence resonance energy transfer

(FRET) between europium cryptate (EuK) as energy donor and cross linked allophycocyanin (XL665) as acceptor. EuK labeled streptavidin (CysBio) binding to Probe I and XL665 labeled anti-His antibody (CysBio) binding to His-integrase are used in the system. Interaction between integrase and Probe I is monitored by energy transfer between the EuK and XL665 in the integrase-probe complex. Displacement of the biotinylated probe from integrase by a compound of the invention results in a loss of fluorescence from the XL665 labeled antibody.

Assay solutions are prepared using an assay buffer consisting of 50 mM HEPES (pH 7.5); 50 mM NaCl; 150 mM KF; 1 mg/ml BSA, 1.0 mM TCEP, 0.05% Tween 20. Assay solution A is prepared with Probe I (30 nM) and His-integrase (300 nM) in assay buffer with 4.5 % DMSO. Assay solutions B is prepared with a compound of the invention diluted to 120  $\mu$ M in assay buffer containing 4.5% DMSO, then serial diluted 11 times in 2-fold steps of the same buffers. Finally, assay solution C is prepared with Streptavidin-EuK and Anti-his XL665 premixed at concentrations of 6 nM and 150 nM respectively in assay buffer.

The reaction mixture was prepared by adding 5  $\mu$ L of each assay solution (solutions A and C with one of the serial dilutions of compound in solution B for each reaction mixture) to a 384-well black round bottom, low volume NBS plates (Corning catalog # 3676) giving a final concentration of 100 nM His-integrase, 10 nM probe, compound of invention (40  $\mu$ M down to 37.5 nM), 50 nM anti-his XL665, 2 nM Strep-EuK and 3% DMSO with a total volume of 15  $\mu$ L. The reaction mixture was incubated at room temperature for one hour. The fluorescence was read on a Victor 1420 Multilable HTS reader at 615 nm and 665 nm.

The compounds of the invention have greater affinity for the HIV integrase target than that of Probe I. However, the increased avidity of the biotinylated probe due to tetramerization with Strep-EuK allows the evaluation of compounds of the invention that have significantly stronger association with HIV integrase.

#### **Example 57: C8166 HIV-1 Luciferase Assay (EC<sub>50</sub>)**

C8166 cells are derived from a human T-lymphotrophic virus type 1 immortalized but nonexpressing line of cord blood lymphocytes (NIH AIDS reagent 404) 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  $\beta$ -mercaptoethanol + 10  $\mu$ g/mL gentamycin) with 5  $\mu$ g/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 12<sup>th</sup> well contains complete media with no inhibitor and serves as the positive control. All samples contain the same concentration of DMSO ( $\leq 0.1\%$  DMSO). A 25  $\mu$ L 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  $\mu$ L 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.  $30 \times 10^6$  cells in 10 mL media/25 cm<sup>2</sup> 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<sub>2</sub> incubator and re-suspended in complete RPMI to give a final concentration of 25,000-cells/175  $\mu$ L. 175  $\mu$ L of cell mix is added to wells of a 96 well microtiter plate containing 25  $\mu$ L 8X inhibitors. 25,000 uninfected C8166-LTRluc cells/well in 200  $\mu$ L complete RPMI are added to the last row for background

control. Cells are incubated at 37 °C in 5% CO<sub>2</sub> incubator for 3 days.

#### Luciferase Assay

50 µL Steady Glo (luciferase substrate T<sub>1/2</sub>=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<sub>50</sub>, slope factor (n) and maximum inhibition (I<sub>max</sub>) by the non-linear regression routine NLIN procedure of SAS using the following equation:

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

Compounds of the invention tested in the cellular assay described above are particularly effective at inhibiting HIV integrase. Compounds of Table 1 were found to have EC<sub>50</sub> values of 300 nM or less. Furthermore, compounds of the invention show unexpected potency across major HIV-1 virus HIV variants. Compounds of Table 1 show unexpected potency in at least four or in all six of the known variants at residues 124 and 125 of HIV-1 virus from infected patients, namely Thr124/Thr125, Ala124/Thr125, Ala124/Ala125, Thr124/Ala125, Asn124/Thr125 and Asn124/Ala125. The results of representative compounds are shown in Table 2.

Table 2

| Compound    | EC <sub>50</sub> (nM)<br>A124/T125 | EC <sub>50</sub> (nM)<br>T124/T125 | EC <sub>50</sub> (nM)<br>T124/A125 | EC <sub>50</sub> (nM)<br>A124/A125 |
|-------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| <b>1008</b> | 11                                 | 59                                 | 49                                 | 55                                 |
| <b>1010</b> | 12                                 | 41                                 | 76                                 | 49                                 |
| <b>1014</b> | 19                                 | 87                                 | 76                                 | 68                                 |

|             |     |     |     |     |
|-------------|-----|-----|-----|-----|
| <b>1018</b> | 35  | 55  | 93  | 110 |
| <b>1023</b> | 12  | 29  | 31  | 37  |
| <b>1038</b> | 3   | 9   | 15  | 8   |
| <b>1052</b> | 28  | 120 | 59  | 64  |
| <b>1059</b> | 3   | 14  | 11  | 9   |
| <b>1136</b> | 91  | 200 | 140 | 170 |
| <b>2001</b> | 71  | 110 | 120 | 67  |
| <b>2002</b> | 9.9 | 19  | 24  | 13  |

#### Generation of viruses with 124/125 variant residues of integrase

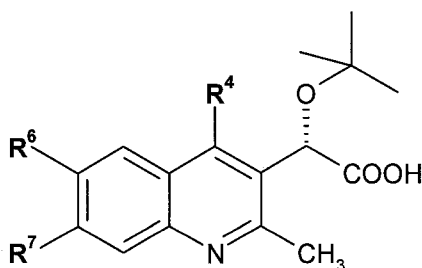
The 2.12 virus with NL4.3 strain of HIV-1 integrase (SEQ ID NO: 1) is used for the Thr124/Thr125 variant integrase residues and HXB2 integrase is introduced into the 2.12 virus for the Ala124/Thr125 variant integrase residues. The remaining variants viruses are generated by site directed mutagenesis of NL4.3 integrase to introduce the Ala124/Ala125, Thr124/Ala125, Asn124/Thr125, or Asn124/Ala125 variants in the 2.12 virus. Molecular biology and generation of virus are performed in a similar manner to Doyon et al. *J Virol.* 70(6):3763-9 (1996). Briefly, site directed mutagenesis is used to introduce silent mutations in the integrase gene of the 2.12 virus. The mutations in NL4.3 integrase introduced unique Cla I and Xba I restriction sites in the 2.12 provirus (using the primers 5' -TTT AGA TGG AAT CGA TAA GGC CCA AGA AG -3' and 5'- CTT CTT GGG CCT TAT CGA TTC CAT CTA AA- 3' to introduce Cla I site and 5'-GGT TTA TTA CAG GGA CTC TAG AGA TCC AGT TTG GA- 3' and 5'- TCC AAA CTG GAT CTC TAG AGT CCC TGT AAT AAA CC - 3' to introduce Xba I site). The 2.12 virus is generated with the Cla I and Xba I restriction sites in integrase replicates and responds to compounds of the invention in a similar manner to the original 2.12 virus. Point mutations at residues 124 and 125 are introduced into NL4.3 integrase in a Pet 28a vector (Novagen) by using the QuikChange site-directed mutagenesis kit (Stratagene). After sequencing to ensure that the desired 124 and/or 125 residue mutations are obtained, the Cla I / Xba I fragment is PCR amplification with Pfu Ultra (Stratagene) and cloned into the unique Cla I /Xba I sites in the 2.12 virus.

### TABLES OF COMPOUNDS

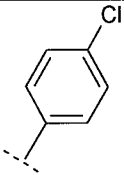
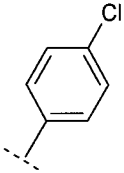
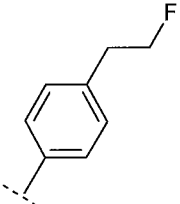
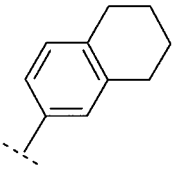
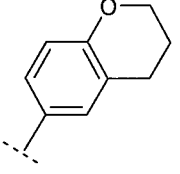
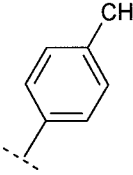
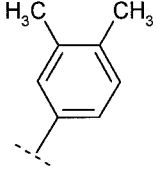
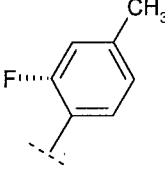
The following tables list compounds of the invention. Compounds of the invention tested in the cellular assay described above in Example 57 are particularly effective at inhibiting HIV integrase. Compounds of Table 1 were found to have EC<sub>50</sub> values of 300 nM or less in at least four or in all six of the known variants at residues 124 and 125 of HIV-1 virus from infected patients, namely Thr124/Thr125, Ala124/Thr125, Ala124/Ala125, Thr124/Ala125, Asn124/Thr125 and Asn124/Ala125.

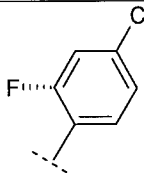
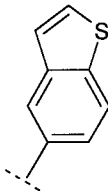
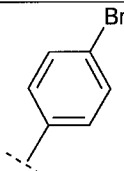
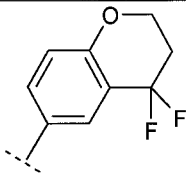
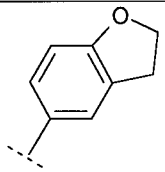
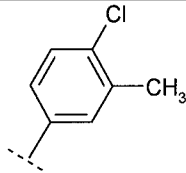
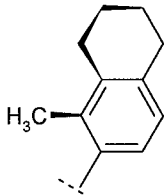
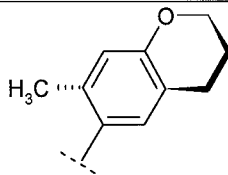
Retention times ( $t_R$ ) for each compound are measured using the standard analytical HPLC conditions described in the Examples. As is well known to one skilled in the art, retention time values are sensitive to the specific measurement conditions. Therefore, even if identical conditions of solvent, 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.

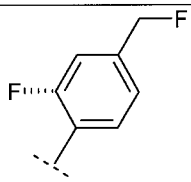
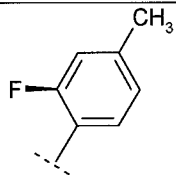
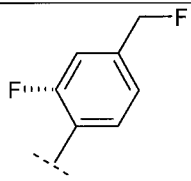
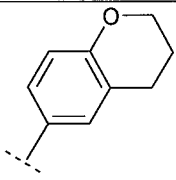
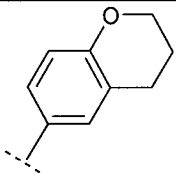
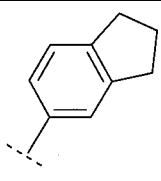
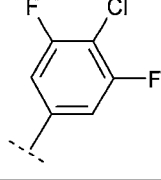
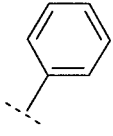
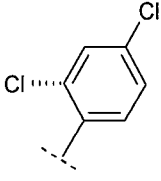
**TABLE 1**

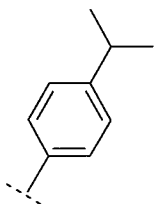
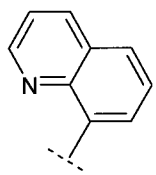
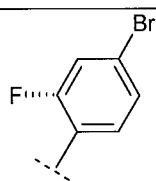
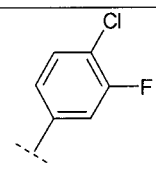
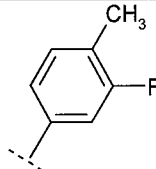
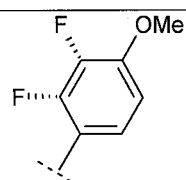
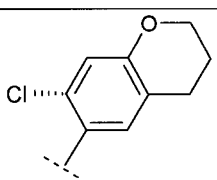
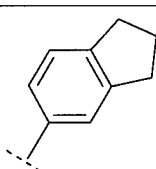


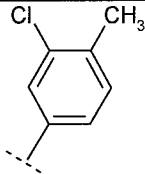
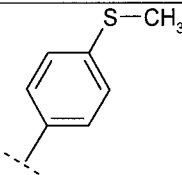
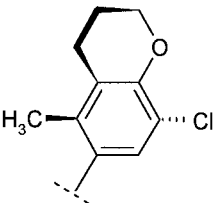
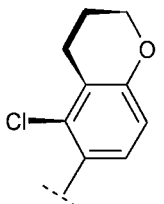
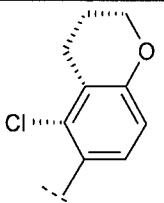
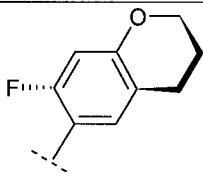
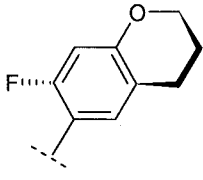
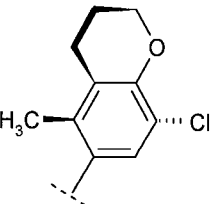
| Cpd  | R <sup>4</sup> | R <sup>6</sup>  | R <sup>7</sup> | $t_R$<br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|----------------|-----------------|----------------|----------------|--------------------------|
| 1001 |                | CH <sub>3</sub> | H              | 4.7            | 398.1 /<br>400.1         |

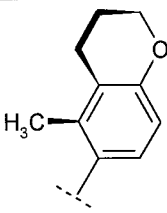
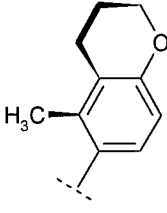
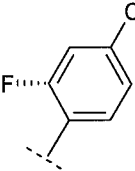
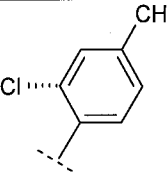
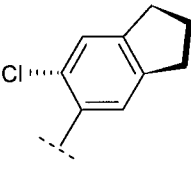
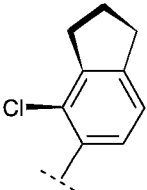
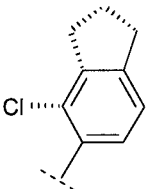
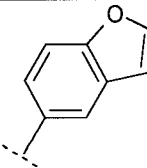
| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|----------------|-----------------|-------------------------|--------------------------|
| 1002 |    | H              | CH <sub>3</sub> | 4.6                     | 398.1 /<br>400.1         |
| 1003 |    | H              | F               | 4.5                     | 402.2 /<br>404.1         |
| 1004 |    | H              | H               | 3.9                     | 396.2                    |
| 1005 |   | H              | H               | 5.1                     | 404.2                    |
| 1006 |  | H              | H               | 4.3                     | 406.2                    |
| 1007 |  | H              | H               | 4.5                     | 364.2                    |
| 1008 |  | H              | H               | 4.8                     | 378.2                    |
| 1009 |  | H              | H               | 4.6                     | 382.1                    |

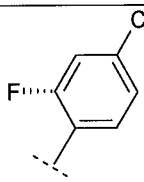
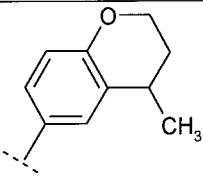
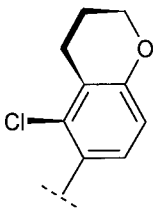
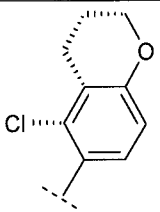
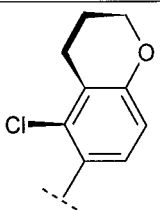
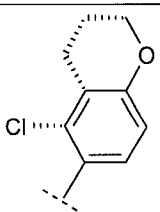
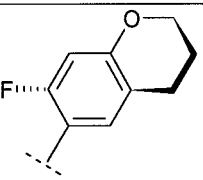
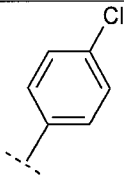
| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|----------------|----------------|-------------------------|--------------------------|
| 1010 |    | H              | H              | 4.8                     | 402.1 /<br>404.1         |
| 1011 |    | H              | H              | 4.7                     | 406.2                    |
| 1012 |    | H              | H              | 4.7                     | 428.0 /<br>430.0         |
| 1013 |   | H              | H              | 3.9                     | 442.1                    |
| 1014 |  | H              | H              | 3.7                     | 392.1                    |
| 1015 |  | H              | H              | 5.0                     | 398.1 /<br>400.1         |
| 1016 |  | H              | H              | 5.6                     | 418.2                    |
| 1017 |  | H              | H              | 5.0                     | 420.2                    |

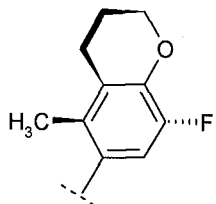
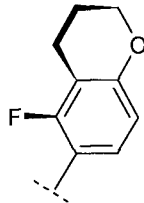
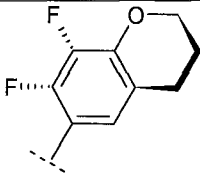
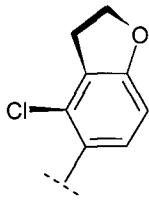
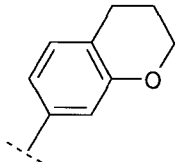
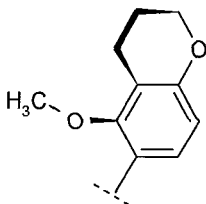
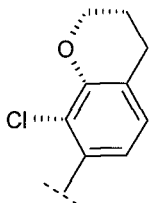
| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup>    |
|------|-------------------------------------------------------------------------------------|----------------|-----------------|-------------------------|-----------------------------|
| 1018 |    | H              | H               | 3.7                     | 400.1                       |
| 1019 |    | H              | H               | 3.7                     | 382.1                       |
| 1020 |    | H              | CH <sub>3</sub> | 4.0                     | 413.2                       |
| 1021 |   | H              | CH <sub>3</sub> | 4.3                     | 420.1                       |
| 1022 |  | F              | H               | 4.9                     | 424.2                       |
| 1023 |  | H              | H               | 4.4                     | 390.1                       |
| 1024 |  | H              | H               | 5.2                     | 420.1 /<br>422.1            |
| 1025 |  | H              | CH <sub>3</sub> | 4.4                     | 364.2                       |
| 1026 |  | H              | CH <sub>3</sub> | 5.3                     | 432.1 /<br>434.1 /<br>436.1 |

| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|----------------|-----------------|-------------------------|--------------------------|
| 1027 |    | H              | CH <sub>3</sub> | 5.5                     | 406.2                    |
| 1028 |    | H              | CH <sub>3</sub> | 3.6                     | 415.2                    |
| 1029 |    | H              | CH <sub>3</sub> | 5.1                     | 460.1 /<br>462.1         |
| 1030 |   | H              | CH <sub>3</sub> | 4.4                     | 416.1 /<br>418.2         |
| 1031 |  | H              | CH <sub>3</sub> | 4.8                     | 396.2                    |
| 1032 |  | H              | CH <sub>3</sub> | 4.8                     | 430.2                    |
| 1033 |  | H              | CH <sub>3</sub> | 5.3                     | 454.1 /<br>456.1         |
| 1034 |  | H              | CH <sub>3</sub> | 4.6                     | 404.2                    |

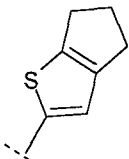
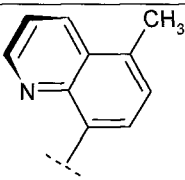
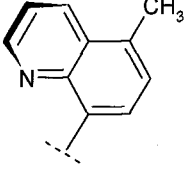
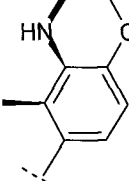
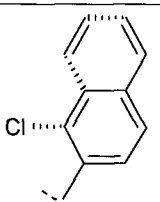
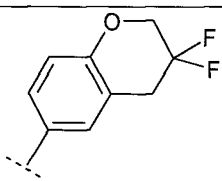
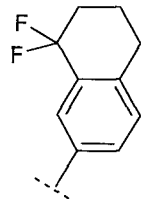
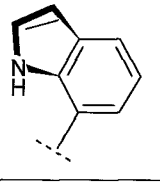
| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|----------------|-----------------|-------------------------|--------------------------|
| 1035 |    | H              | H               | 4.9                     | 398.1 /<br>400.1         |
| 1036 |    | H              | CH <sub>3</sub> | 4.8                     | 410.2                    |
| 1037 |    | H              | H               | 5.3                     | 454.2 /<br>456.2         |
| 1038 |   | H              | H               | 4.9                     | 440.2 /<br>442.2         |
| 1039 |  | H              | H               | 5.1                     | 440.2 /<br>442.2         |
| 1040 |  | H              | H               | 4.1                     | 424.1                    |
| 1041 |  | H              | CH <sub>3</sub> | 4.3                     | 438.2                    |
| 1042 |  | H              | CH <sub>3</sub> | 5.6                     | 468.1 /<br>470.1         |

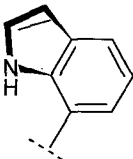
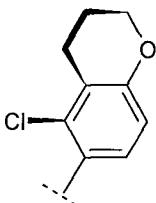
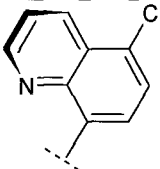
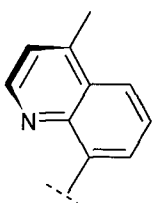
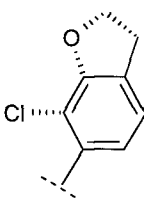
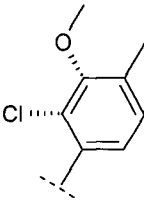
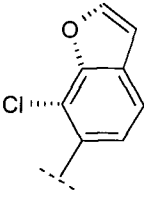
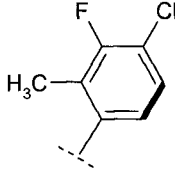
| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup>  | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|-----------------|----------------|-------------------------|--------------------------|
| 1043 |    | CH <sub>3</sub> | H              | 5.2                     | 434.2                    |
| 1044 |    | H               | H              | 4.9                     | 420.2                    |
| 1045 |    | CH <sub>3</sub> | H              | 4.4                     | 416.1 /<br>418.1         |
| 1046 |   | H               | H              | 4.8                     | 398.1 /<br>400.1         |
| 1047 |  | H               | H              | 4.7                     | 424.1                    |
| 1048 |  | H               | H              | 4.5                     | 424.1 /<br>426.1         |
| 1049 |  | H               | H              | 4.8                     | 424.1 /<br>426.1         |
| 1050 |  | H               | H              | 3.9                     | 390.1                    |

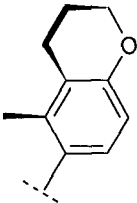
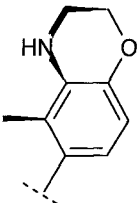
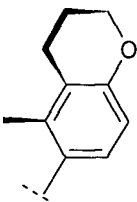
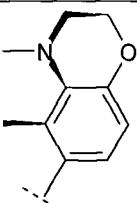
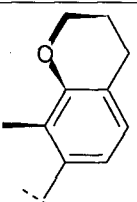
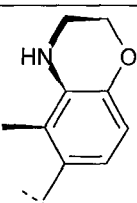
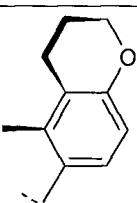
| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup>                  | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|---------------------------------|-----------------|-------------------------|--------------------------|
| 1051 |    | H                               | CH <sub>3</sub> | 4.3                     | 416.1 /<br>418.1         |
| 1052 |    | H                               | H               | 4.1                     | 420.2                    |
| 1053 |    | CH <sub>3</sub>                 | H               | 5.1                     | 454.1 /<br>456.1         |
| 1054 |   | CH <sub>3</sub>                 | H               | 5.4                     | 454.1 /<br>456.1         |
| 1055 |  | H                               | CH <sub>3</sub> | 5.2                     | 454.1 /<br>456.1         |
| 1056 |  | H                               | CH <sub>3</sub> | 5.4                     | 454.1 /<br>456.1         |
| 1057 |  | CH <sub>3</sub>                 | H               | 5.1                     | 438.3                    |
| 1058 |  | CH <sub>2</sub> CH <sub>3</sub> | H               | 5.5                     | 412.2 /<br>414.2         |

| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|----------------|----------------|-------------------------|--------------------------|
| 1059 |    | H              | H              | 4.9                     | 438.2                    |
| 1060 |    | H              | H              | 3.7                     | 424.4                    |
| 1061 |    | H              | H              | 3.9                     | 442.2                    |
| 1062 |  | H              | H              | 4.5                     | 426.2 /<br>428.2         |
| 1063 |  | H              | H              | 3.7                     | 406.2                    |
| 1064 |  | H              | H              | 4.8                     | 436.3                    |
| 1065 |  | H              | H              | 3.8                     | 440.2 /<br>442.1         |

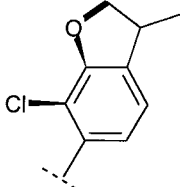
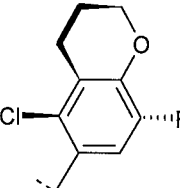
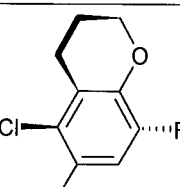
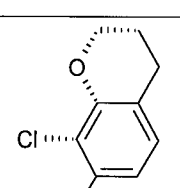
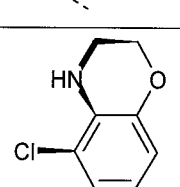
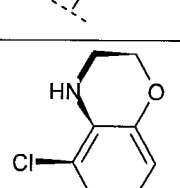
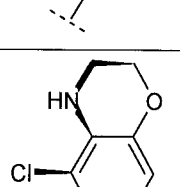
| Cpd  | R <sup>4</sup> | R <sup>6</sup> | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|----------------|----------------|----------------|-------------------------|--------------------------|
| 1066 |                | H              | H              | 4.6                     | 406.2                    |
| 1067 |                | H              | H              | 4.1                     | 440.2                    |
| 1068 |                | H              | H              | 4.9                     | 420.2                    |
| 1069 |                | H              | H              | 4.6                     | 406.2                    |
| 1070 |                | H              | H              | 4.4                     | 434.1 /<br>436.1         |
| 1071 |                | H              | H              | 5.0                     | 424.1 /<br>426.1         |
| 1072 |                | H              | H              | 4.7                     | 424.1 /<br>426.1         |
| 1073 |                | H              | H              | 4.9                     | 424.1 /<br>426.1         |

| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|----------------|-----------------|-------------------------|--------------------------|
| 1074 |    | H              | H               | 5.0                     | 396.2                    |
| 1075 |    | H              | H               | 3.6                     | 415.3                    |
| 1076 |    | H              | CH <sub>3</sub> | 3.9                     | 429.2                    |
| 1077 |   | H              | H               | 3.8                     | 421.2                    |
| 1078 |  | H              | CH <sub>3</sub> | 5.7                     | 448.1 /<br>450.1         |
| 1079 |  | H              | H               | 5.2                     | 442.2                    |
| 1080 |  | H              | H               | 5.4                     | 440.1                    |
| 1081 |  | H              | H               | 4.6                     | 398.2                    |

| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|----------------|-----------------|-------------------------|--------------------------|
| 1082 |    | H              | CH <sub>3</sub> | 4.9                     | 403.2                    |
| 1083 |    | F              | H               | 5.6                     | 458.1 /<br>460.1         |
| 1084 |    | H              | CH <sub>3</sub> | 4.5                     | 449.2 /<br>451.2         |
| 1085 |   | H              | CH <sub>3</sub> | 3.4                     | 429.3                    |
| 1086 |  | H              | H               | 5.0                     | 426.2 /<br>428.2         |
| 1087 |  | H              | H               | 4.8                     | 428.2 /<br>430.2         |
| 1088 |  | H              | H               | 4.8                     | 424.1 /<br>426.1         |
| 1089 |  | H              | H               | 4.9                     | 416.2 /<br>418.2         |

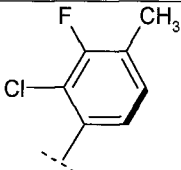
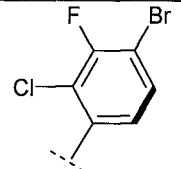
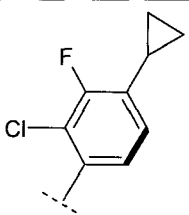
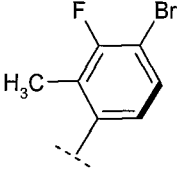
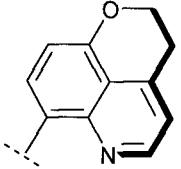
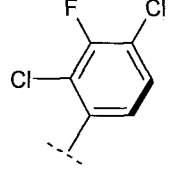
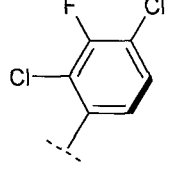
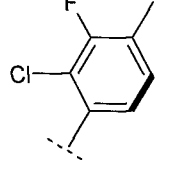
| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup>  | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|-----------------|-----------------|-------------------------|--------------------------|
| 1090 |    | F               | H               | 5.5                     | 438.2                    |
| 1091 |    | Cl              | H               | 4.8                     | 455.2 /<br>457.2         |
| 1092 |   | Cl              | H               | 5.4                     | 454.2 /<br>456.2         |
| 1093 |  | H               | H               | 4.1                     | 434.2                    |
| 1094 |  | H               | H               | 5.5                     | 420.2                    |
| 1095 |  | H               | CH <sub>3</sub> | 4.6                     | 435.2                    |
| 1096 |  | CH <sub>3</sub> | CH <sub>3</sub> | 5.3                     | 448.3                    |

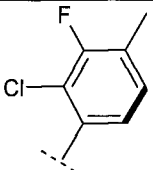
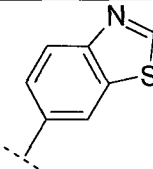
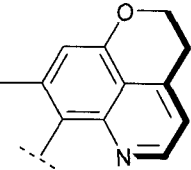
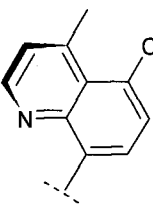
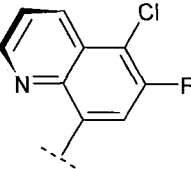
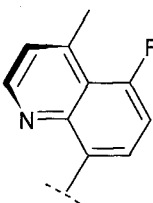
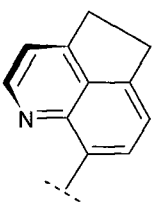
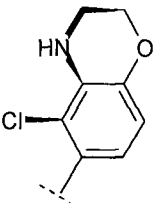
| Cpd  | R <sup>4</sup> | R <sup>6</sup>  | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|----------------|-----------------|----------------|-------------------------|--------------------------|
| 1097 |                | H               | H              | 4.3                     | 455.2 /<br>457.2         |
| 1098 |                | H               | H              | 5.5                     | 476.1 /<br>478.1         |
| 1099 |                | F               | H              | 4.4                     | 439.2                    |
| 1100 |                | CH <sub>3</sub> | H              | 4.5                     | 435.2                    |
| 1101 |                | H               | H              | 3.9                     | 432.2                    |
| 1102 |                | H               | H              | 4.4                     | 441.2 /<br>443.1         |
| 1103 |                | H               | H              | 4.1                     | 419.3                    |

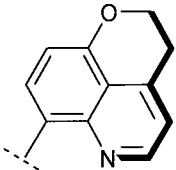
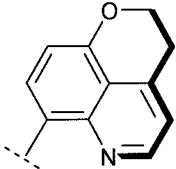
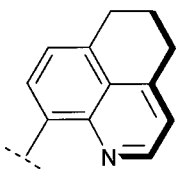
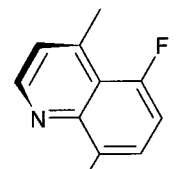
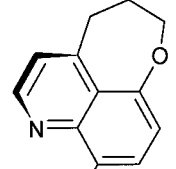
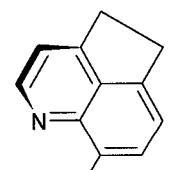
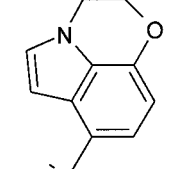
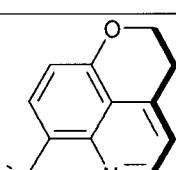
| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup>  | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup>    |
|------|-------------------------------------------------------------------------------------|-----------------|----------------|-------------------------|-----------------------------|
| 1104 |    | H               | H              | 4.5                     | 440.2 /<br>442.1            |
| 1105 |    | H               | H              | 5.1                     | 458.2 /<br>460.2            |
| 1106 |    | Cl              | H              | 5.8                     | 492.1 /<br>494.1 /<br>496.1 |
| 1107 |  | Cl              | H              | 5.6                     | 474.2 /<br>476.2            |
| 1108 |  | F               | H              | 4.2                     | 459.2 /<br>461.1            |
| 1109 |  | Cl              | H              | 4.7                     | 475.1 /<br>477.1 /<br>479.1 |
| 1110 |  | CH <sub>3</sub> | H              | 4.6                     | 455.2 /<br>457.2            |

| Cpd  | R <sup>4</sup> | R <sup>6</sup> | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup>    |
|------|----------------|----------------|-----------------|-------------------------|-----------------------------|
| 1111 |                | H              | CH <sub>3</sub> | 4.5                     | 455.2 /<br>457.2            |
| 1112 |                | H              | H               | 5.0                     | 436.1 /<br>438.1 /<br>440.1 |
| 1113 |                | H              | H               | 5.4                     | 432.1 /<br>434.1 /<br>438.1 |
| 1114 |                | H              | H               | 4.4                     | 384.1 /<br>386.1            |
| 1115 |                | H              | H               | 4.3                     | 449.3                       |
| 1116 |                | H              | H               | 4.4                     | 469.2 /<br>471.2            |
| 1117 |                | H              | H               | 4.5                     | 402.1 /<br>404.1            |
| 1118 |                | F              | CH <sub>3</sub> | 4.4                     | 453.2                       |

| Cpd  | R <sup>4</sup> | R <sup>6</sup> | R <sup>7</sup>  | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup>    |
|------|----------------|----------------|-----------------|-------------------------|-----------------------------|
| 1119 |                | F              | CH <sub>3</sub> | 5.4                     | 473.2 /<br>475.2            |
| 1120 |                | H              | H               | 4.6                     | 402.1 /<br>404.1            |
| 1121 |                | H              | H               | 4.4                     | 382.2                       |
| 1122 |                | F              | CH <sub>3</sub> | 5.5                     | 452.3                       |
| 1123 |                | H              | CH <sub>3</sub> | 5.3                     | 494.0 /<br>496.0 /<br>498.0 |
| 1124 |                | H              | H               | 4.5                     | 402.2 /<br>404.2            |
| 1125 |                | H              | H               | 5.1                     | 480.1 /<br>482.1 /<br>484.1 |
| 1126 |                | Cl             | H               | 5.9                     | 514.0 /<br>516.0 /<br>518.0 |

| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>   | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup>    |
|------|-------------------------------------------------------------------------------------|----------------|------------------|-------------------------|-----------------------------|
| 1127 |    | H              | H                | 4.9                     | 416.2 /<br>418.2            |
| 1128 |    | F              | H                | 5.4                     | 498.0 /<br>500.0 /<br>502.0 |
| 1129 |    | H              | H                | 5.3                     | 442.2 /<br>444.2            |
| 1130 |   | H              | H                | 4.9                     | 460.1 /<br>462.1            |
| 1131 |  | H              | -CH <sub>3</sub> | 3.6                     | 457.3                       |
| 1132 |  | H              | CH <sub>3</sub>  | 5.2                     | 450.1 /<br>452.1 /<br>454.1 |
| 1133 |  | F              | H                | 5.4                     | 454.1 /<br>456.1 /<br>458.1 |
| 1134 |  | F              | H                | 5.2                     | 434.2 /<br>436.2            |

| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup>    |
|------|-------------------------------------------------------------------------------------|----------------|----------------|-------------------------|-----------------------------|
| 1135 |    | Cl             | H              | 5.6                     | 450.1 /<br>452.1 /<br>454.1 |
| 1136 |    | H              | H              | 3.0                     | 407.1                       |
| 1137 |    | H              | Me             | 3.7                     | 471.3                       |
| 1138 |   | H              | Me             | 5.0                     | 463.2 /<br>465.2            |
| 1139 |  | H              | Me             | 4.8                     | 468.2 /<br>469.2            |
| 1140 |  | H              | Me             | 4.4                     | 447.3                       |
| 1141 |  | H              | Me             | 3.1                     | 441.2                       |
| 1142 |  | H              | Cl             | 5.4                     | 475.1 /<br>477.1 /<br>479.1 |

| Cpd  | R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|----------------|----------------|-------------------------|--------------------------|
| 1143 |    | H              | Cl             | 3.1                     | 477.2 /<br>479.2         |
| 1144 |    | H              | H              | 3.7                     | 443.2                    |
| 1145 |    | H              | H              | 3.2                     | 441.3                    |
| 1146 |   | H              | H              | 4.1                     | 433.3                    |
| 1147 |  | H              | H              | 3.8                     | 457.2                    |
| 1148 |  | H              | H              | 2.8                     | 472.2                    |
| 1149 |  | H              | H              | 4.5                     | 430.0                    |
| 1150 |  | Me             | H              | 3.7                     | 457.2                    |

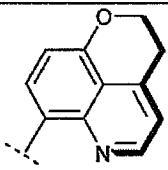
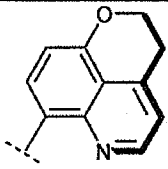
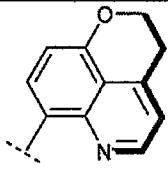
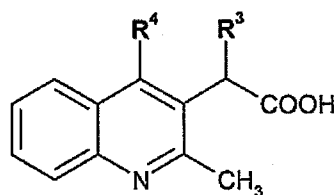
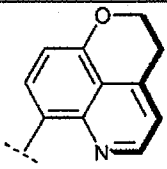
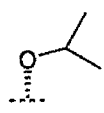
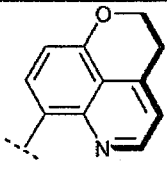
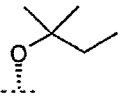
| Cpd  | R <sup>4</sup>                                                                    | R <sup>6</sup> | R <sup>7</sup> | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-----------------------------------------------------------------------------------|----------------|----------------|-------------------------|--------------------------|
| 1151 |  | Cl             | H              | 3.0                     | 477.3 /<br>479.3         |
| 1152 |  | F              | H              | 2.8                     | 461.3                    |
| 1153 |  | F              | Me             | 2.9                     | 475.1                    |

TABLE 2



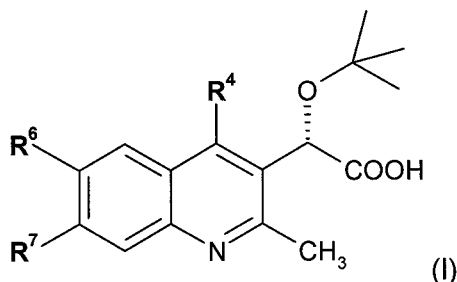
| Cpd  | R <sup>4</sup>                                                                      | R <sup>3</sup>                                                                       | t <sub>R</sub><br>(min) | MS<br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------|--------------------------|
| 2001 |  |   | 3.0                     | 429.2                    |
| 2002 |  |  | 2.9                     | 457.3                    |

Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, 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 compounds of formula (I):



wherein

**R<sup>4</sup>** is aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>1-6</sub>)haloalkyl, (C<sub>3-7</sub>)cycloalkyl, -OH, -O(C<sub>1-6</sub>)alkyl, -SH, -S(C<sub>1-6</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>; wherein the (C<sub>1-6</sub>)alkyl is optionally substituted with hydroxy, cyano or oxo;

**R<sup>6</sup>** and **R<sup>7</sup>** are each independently selected from H, halo, (C<sub>1-6</sub>)alkyl and (C<sub>1-6</sub>)haloalkyl;

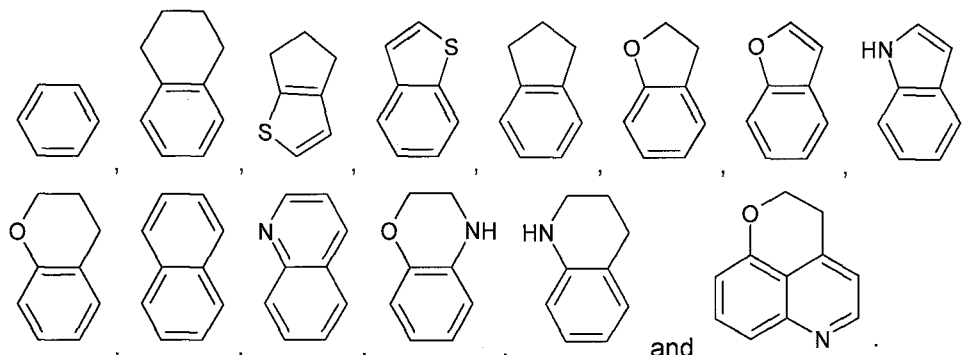
wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S;

or a salt or an ester thereof.

2. The compound according to claim 1 wherein **R<sup>4</sup>** is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>1-6</sub>)haloalkyl, (C<sub>3-7</sub>)cycloalkyl, -OH, -O(C<sub>1-6</sub>)alkyl, -SH, -S(C<sub>1-6</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>.
3. The compound according to claim 2 wherein **R<sup>4</sup>** is **Het** optionally substituted with 1 to 2 substituents each independently selected from halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl.
4. The compound according to claim 3 wherein **R<sup>4</sup>** is **Het** optionally substituted

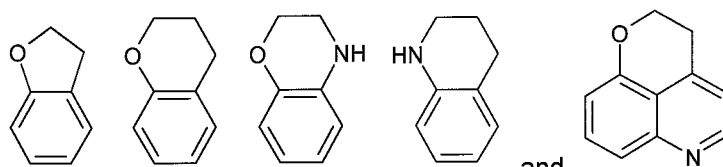
with 1 to 2 substituents each independently selected from Cl, F, CH<sub>3</sub> and CH<sub>2</sub>CH<sub>3</sub> wherein said **Het** is defined as a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 2 heteroatoms, each independently selected from O, N and S.

5. The compound according to claim 3 wherein **R**<sup>4</sup> is **Het** optionally substituted with 1 to 2 substituents each independently selected from halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl, wherein said **Het** is defined as a 9- or 10-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 2 heteroatoms, each independently selected from O, N and S.
6. The compound according to claim 1 wherein **R**<sup>4</sup> is phenyl optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)haloalkyl, -O(C<sub>1-4</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>.
7. The compound according to claim 1 wherein **R**<sup>4</sup> is aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>1-6</sub>)haloalkyl, (C<sub>3-7</sub>)cycloalkyl, -OH, -O(C<sub>1-6</sub>)alkyl, -SH, -S(C<sub>1-6</sub>)alkyl, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>)alkyl and -N((C<sub>1-6</sub>)alkyl)<sub>2</sub>; wherein the (C<sub>1-6</sub>)alkyl is optionally substituted with hydroxy, cyano or oxo; and wherein the aryl is not monosubstituted at the para position.
8. The compound according to claim 1 wherein **R**<sup>4</sup> is selected from:



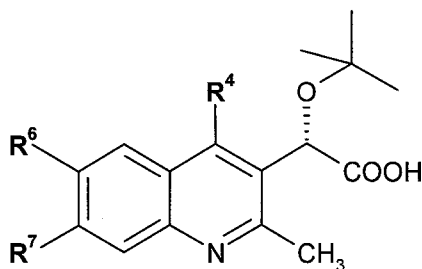
optionally substituted 1 to 3 times with halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl.

- 9.** The compound according to claim 8 wherein  $R^4$  is selected from:

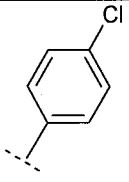
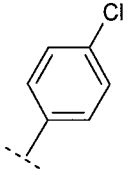
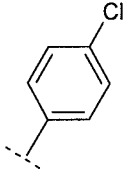
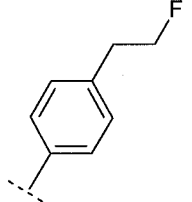
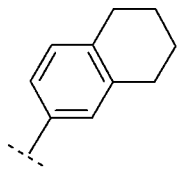
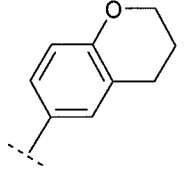
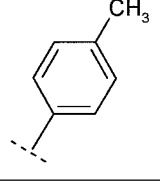
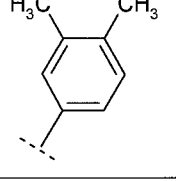


optionally substituted 1 to 2 times with halo, (C<sub>1-3</sub>)alkyl and O-(C<sub>1-3</sub>)alkyl.

10. The compound according to any one of claims 1 to 9 wherein **R**<sup>6</sup> is H, halo or (C<sub>1-3</sub>)alkyl.
11. The compound according to claim 10 wherein **R**<sup>6</sup> is H, F, Cl or (C<sub>1-2</sub>)alkyl.
12. The compound according to claim 11 wherein **R**<sup>6</sup> is H or CH<sub>3</sub>.
13. The compound according to claim 12 wherein **R**<sup>6</sup> is H.
14. The compound according to any one of claims 1 to 13 wherein **R**<sup>7</sup> is H, halo or (C<sub>1-3</sub>)alkyl.
15. The compound according to claim 14 wherein **R**<sup>7</sup> is H, F, Cl or (C<sub>1-2</sub>)alkyl.
16. The compound according to claim 15 wherein **R**<sup>7</sup> is H, F, Cl or CH<sub>3</sub>.
17. The compound according to claim 16 wherein **R**<sup>7</sup> is H or CH<sub>3</sub>.
18. The compound according to claim 17 wherein **R**<sup>7</sup> is H.
19. The compound according to claim 1 having the following formula:



wherein **R**<sup>4</sup>, **R**<sup>6</sup> and **R**<sup>7</sup> are defined as:

| $R^4$                                                                               | $R^6$  | $R^7$  |
|-------------------------------------------------------------------------------------|--------|--------|
|    | $CH_3$ | H      |
|    | H      | $CH_3$ |
|    | H      | F      |
|   | H      | H      |
|  | H      | H      |
|  | H      | H      |
|  | H      | H      |
|  | H      | H      |

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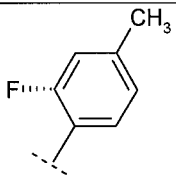
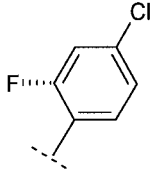
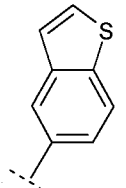
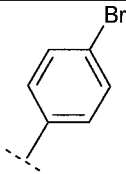
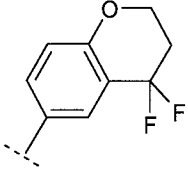
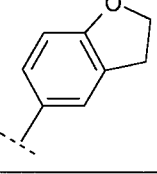
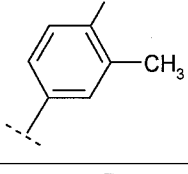
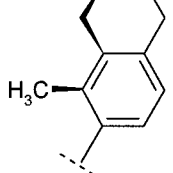
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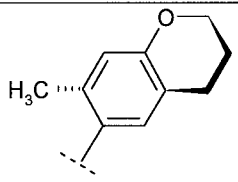
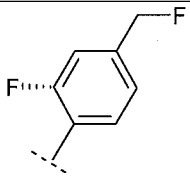
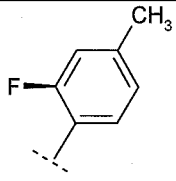
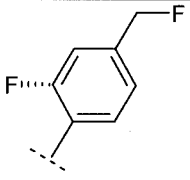
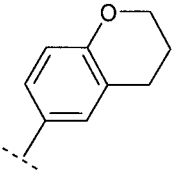
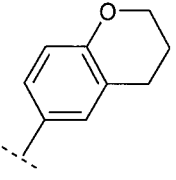
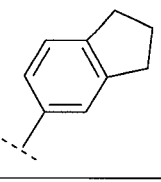
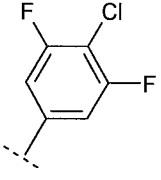
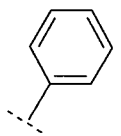
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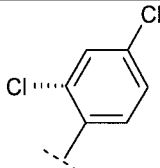
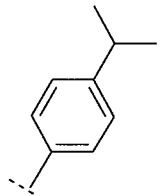
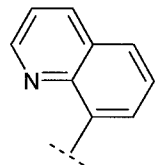
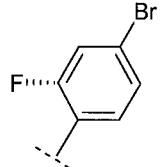
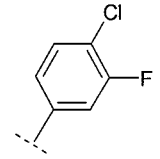
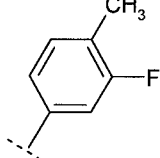
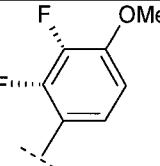
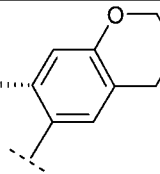
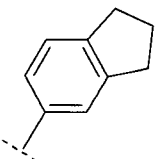
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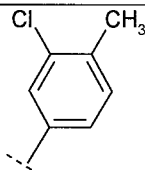
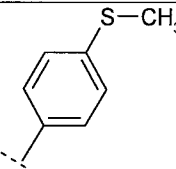
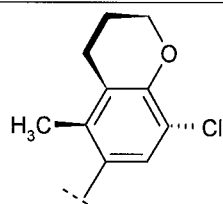
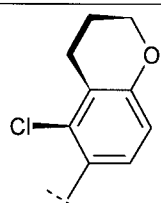
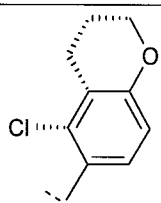
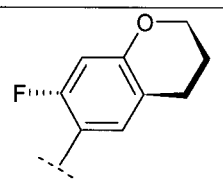
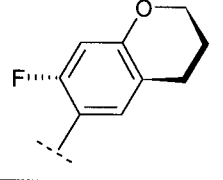
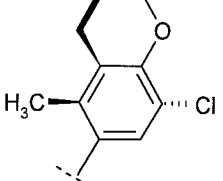
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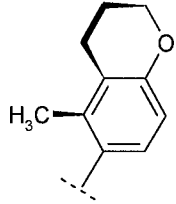
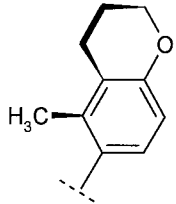
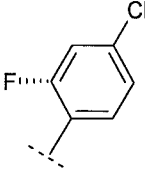
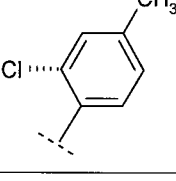
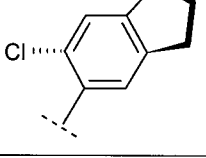
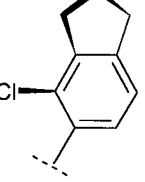
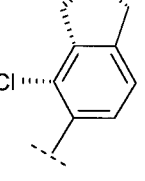
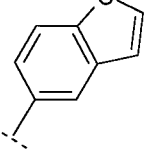
;

| $R^4$                                                                               | $R^6$ | $R^7$ |   |
|-------------------------------------------------------------------------------------|-------|-------|---|
|    | H     | H     | ; |
|    | H     | H     | ; |
|    | H     | H     | ; |
|   | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |

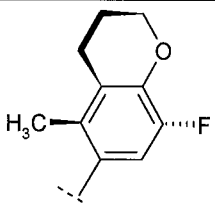
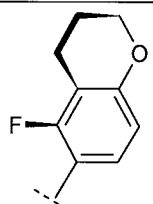
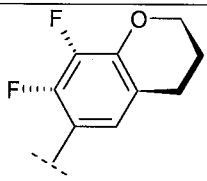
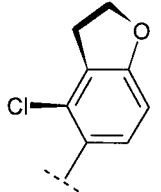
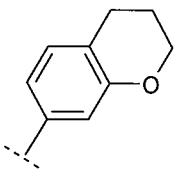
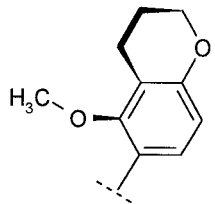
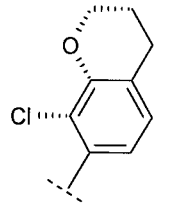
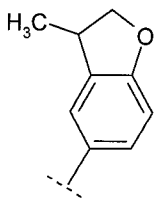
| $R^4$                                                                               | $R^6$ | $R^7$           |   |
|-------------------------------------------------------------------------------------|-------|-----------------|---|
|    | H     | H               | ; |
|    | H     | H               | ; |
|    | H     | H               | ; |
|   | H     | CH <sub>3</sub> | ; |
|  | H     | CH <sub>3</sub> | ; |
|  | F     | H               | ; |
|  | H     | H               | ; |
|  | H     | H               | ; |
|  | H     | CH <sub>3</sub> | ; |

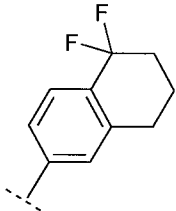
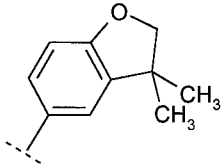
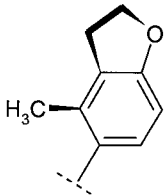
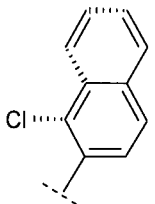
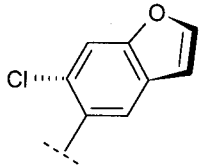
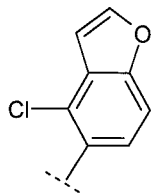
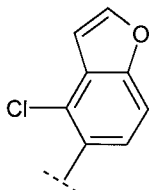
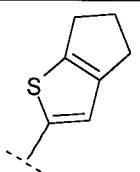
| $R^4$                                                                               | $R^6$ | $R^7$           |   |
|-------------------------------------------------------------------------------------|-------|-----------------|---|
|    | H     | CH <sub>3</sub> | ; |
|    | H     | CH <sub>3</sub> | ; |
|    | H     | CH <sub>3</sub> | ; |
|   | H     | CH <sub>3</sub> | ; |
|  | H     | CH <sub>3</sub> | ; |
|  | H     | CH <sub>3</sub> | ; |
|  | H     | CH <sub>3</sub> | ; |
|  | H     | CH <sub>3</sub> | ; |
|  | H     | CH <sub>3</sub> | ; |

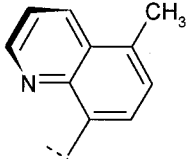
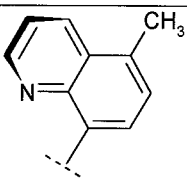
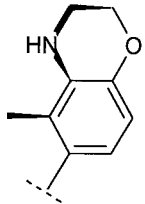
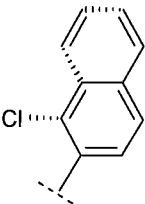
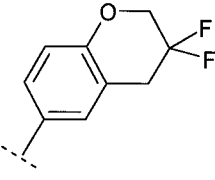
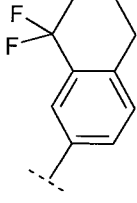
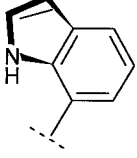
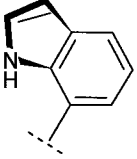
| <b>R<sup>4</sup></b>                                                                | <b>R<sup>6</sup></b> | <b>R<sup>7</sup></b> |   |
|-------------------------------------------------------------------------------------|----------------------|----------------------|---|
|    | H                    | H                    | ; |
|    | H                    | CH <sub>3</sub>      | ; |
|    | H                    | H                    | ; |
|   | H                    | H                    | ; |
|  | H                    | H                    | ; |
|  | H                    | H                    | ; |
|  | H                    | CH <sub>3</sub>      | ; |
|  | H                    | CH <sub>3</sub>      | ; |

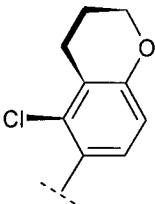
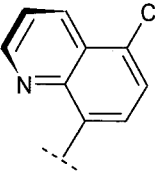
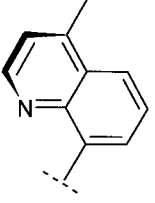
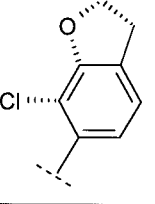
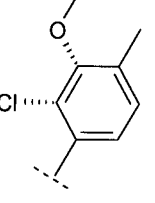
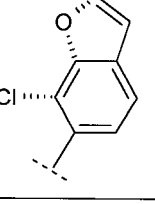
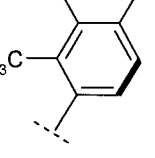
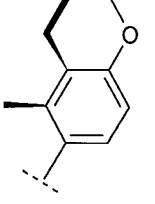
| $R^4$                                                                               | $R^6$  | $R^7$ |   |
|-------------------------------------------------------------------------------------|--------|-------|---|
|    | $CH_3$ | H     | ; |
|    | H      | H     | ; |
|    | $CH_3$ | H     | ; |
|   | H      | H     | ; |
|  | H      | H     | ; |
|  | H      | H     | ; |
|  | H      | H     | ; |
|  | H      | H     | ; |

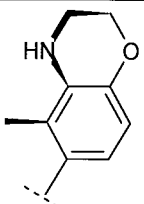
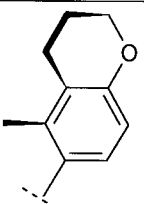
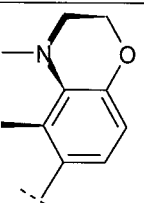
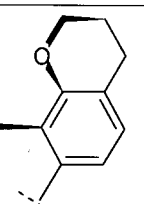
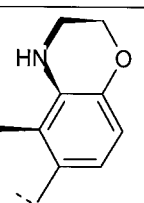
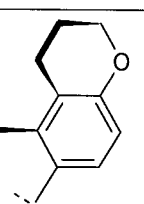
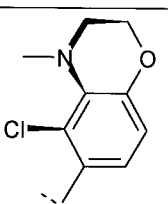
| $R^4$ | $R^6$                           | $R^7$           |   |
|-------|---------------------------------|-----------------|---|
|       | H                               | CH <sub>3</sub> | ; |
|       | H                               | H               | ; |
|       | CH <sub>3</sub>                 | H               | ; |
|       | CH <sub>3</sub>                 | H               | ; |
|       | H                               | CH <sub>3</sub> | ; |
|       | H                               | CH <sub>3</sub> | ; |
|       | CH <sub>3</sub>                 | H               | ; |
|       | CH <sub>2</sub> CH <sub>3</sub> | H               | ; |

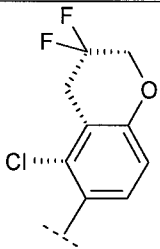
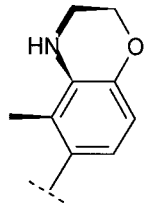
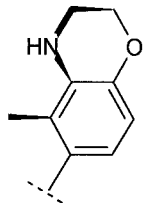
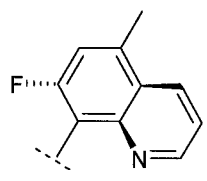
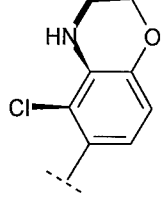
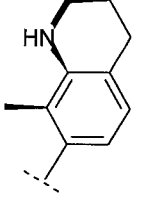
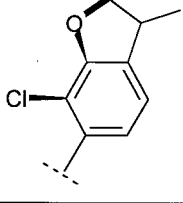
| $R^4$                                                                               | $R^6$ | $R^7$ |   |
|-------------------------------------------------------------------------------------|-------|-------|---|
|    | H     | H     | ; |
|    | H     | H     | ; |
|    | H     | H     | ; |
|   | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |

| $R^4$                                                                               | $R^6$ | $R^7$ |   |
|-------------------------------------------------------------------------------------|-------|-------|---|
|    | H     | H     | ; |
|    | H     | H     | ; |
|    | H     | H     | ; |
|   | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |
|  | H     | H     | ; |

| R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  |   |
|-------------------------------------------------------------------------------------|----------------|-----------------|---|
|    | H              | H               | ; |
|    | H              | CH <sub>3</sub> | ; |
|    | H              | H               | ; |
|   | H              | CH <sub>3</sub> | ; |
|  | H              | H               | ; |
|  | H              | H               | ; |
|  | H              | H               | ; |
|  | H              | CH <sub>3</sub> | ; |

| R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  |   |
|-------------------------------------------------------------------------------------|----------------|-----------------|---|
|    | F              | H               | ; |
|    | H              | CH <sub>3</sub> | ; |
|    | H              | CH <sub>3</sub> | ; |
|   | H              | H               | ; |
|  | H              | H               | ; |
|  | H              | H               | ; |
|  | H              | H               | ; |
|  | F              | H               | ; |

| $R^4$                                                                               | $R^6$           | $R^7$           |
|-------------------------------------------------------------------------------------|-----------------|-----------------|
|    | Cl              | H               |
|    | Cl              | H               |
|    | H               | H               |
|   | H               | H               |
|  | H               | CH <sub>3</sub> |
|  | CH <sub>3</sub> | CH <sub>3</sub> |
|  | H               | H               |

| R <sup>4</sup>                                                                      | R <sup>6</sup>  | R <sup>7</sup> |
|-------------------------------------------------------------------------------------|-----------------|----------------|
|    | H               | H              |
|    | F               | H              |
|   | CH <sub>3</sub> | H              |
|  | H               | H              |
|  | H               | H              |
|  | H               | H              |
|  | H               | H              |

;

;

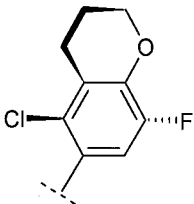
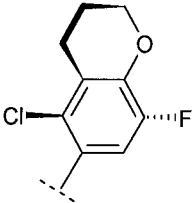
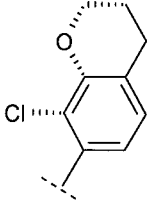
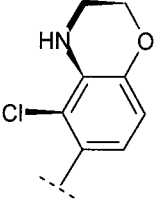
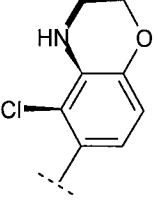
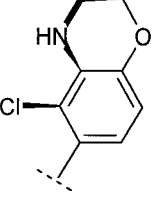
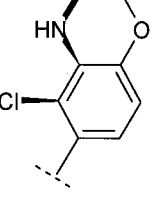
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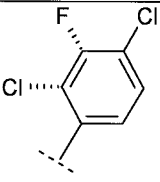
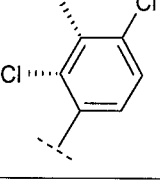
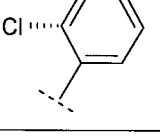
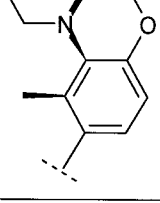
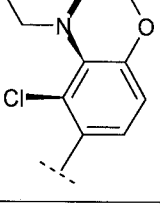
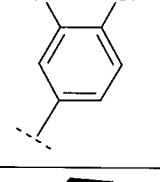
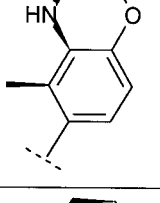
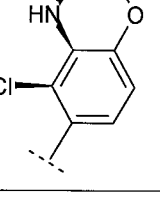
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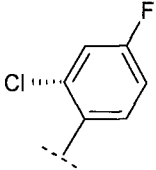
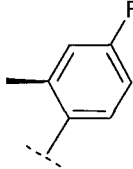
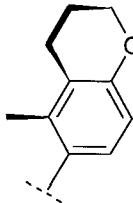
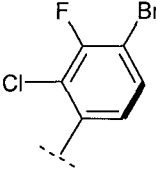
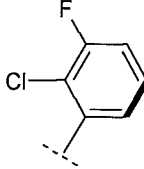
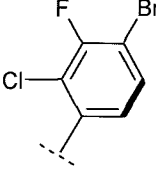
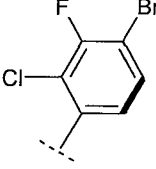
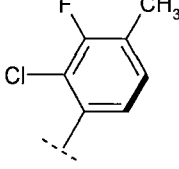
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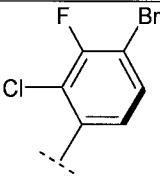
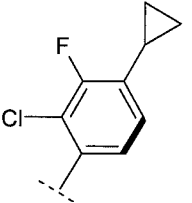
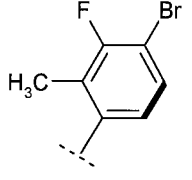
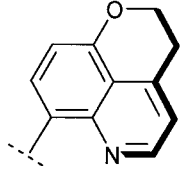
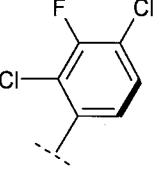
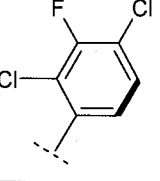
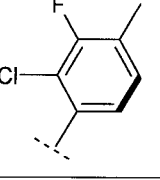
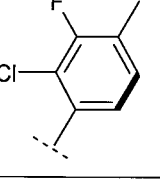
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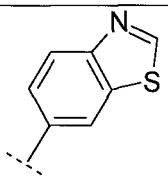
;

| R <sup>4</sup>                                                                      | R <sup>6</sup>  | R <sup>7</sup>  |
|-------------------------------------------------------------------------------------|-----------------|-----------------|
|    | H               | H               |
|    | Cl              | H               |
|    | Cl              | H               |
|  | F               | H               |
|  | Cl              | H               |
|  | CH <sub>3</sub> | H               |
|  | H               | CH <sub>3</sub> |

| R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  |   |
|-------------------------------------------------------------------------------------|----------------|-----------------|---|
|    | H              | H               | ; |
|    | H              | H               | ; |
|    | H              | H               | ; |
|   | H              | H               | ; |
|  | H              | H               | ; |
|  | H              | H               | ; |
|  | F              | CH <sub>3</sub> | ; |
|  | F              | CH <sub>3</sub> | ; |

| R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup>  |   |
|-------------------------------------------------------------------------------------|----------------|-----------------|---|
|    | H              | H               | ; |
|    | H              | H               | ; |
|    | F              | CH <sub>3</sub> | ; |
|   | H              | CH <sub>3</sub> | ; |
|  | H              | H               | ; |
|  | H              | H               | ; |
|  | Cl             | H               | ; |
|  | H              | H               | ; |

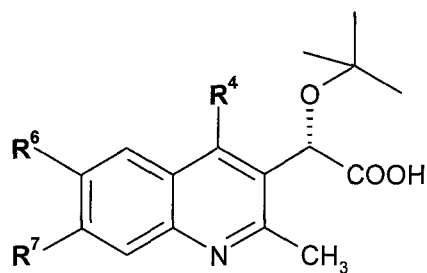
| $R^4$                                                                               | $R^6$ | $R^7$            |   |
|-------------------------------------------------------------------------------------|-------|------------------|---|
|    | F     | H                | ; |
|    | H     | H                | ; |
|    | H     | H                | ; |
|   | H     | -CH <sub>3</sub> | ; |
|  | H     | CH <sub>3</sub>  | ; |
|  | F     | H                | ; |
|  | F     | H                | ; |
|  | Cl    | H                | ; |

| $R^4$                                                                             | $R^6$ | $R^7$ |
|-----------------------------------------------------------------------------------|-------|-------|
|  | H     | H     |

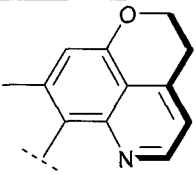
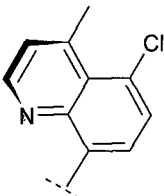
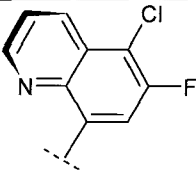
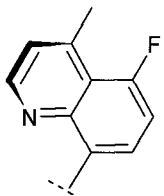
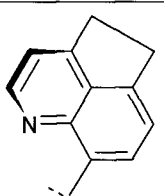
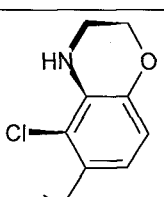
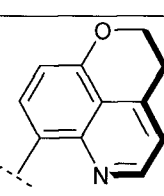
and

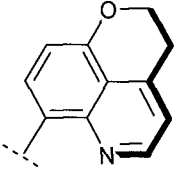
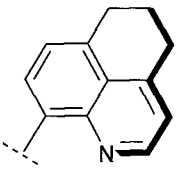
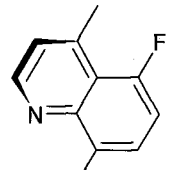
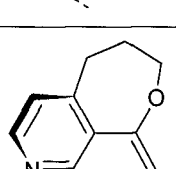
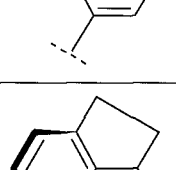
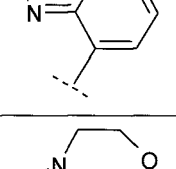
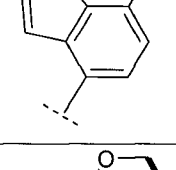
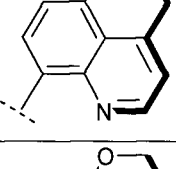
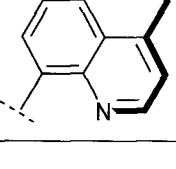
pharmaceutically acceptable salts or esters thereof.

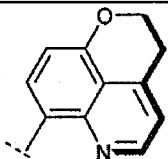
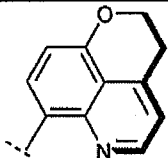
20. The compound according to claim 1 having the following formula:



wherein  $R^4$ ,  $R^6$  and  $R^7$  are defined as:

| R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup> |
|-------------------------------------------------------------------------------------|----------------|----------------|
|    | H              | Me             |
|    | H              | Me             |
|    | H              | Me             |
|   | H              | Me             |
|  | H              | Me             |
|  | H              | Cl             |
|  | H              | Cl             |

| R <sup>4</sup>                                                                      | R <sup>6</sup> | R <sup>7</sup> |
|-------------------------------------------------------------------------------------|----------------|----------------|
|    | H              | H              |
|    | H              | H              |
|    | H              | H              |
|   | H              | H              |
|  | H              | H              |
|  | H              | H              |
|  | H              | H              |
|  | Me             | H              |
|  | Cl             | H              |

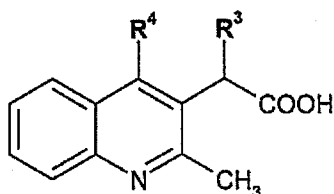
| R <sup>4</sup>                                                                    | R <sup>6</sup> | R <sup>7</sup> |
|-----------------------------------------------------------------------------------|----------------|----------------|
|  | F              | H              |
|  | F              | Me             |

;

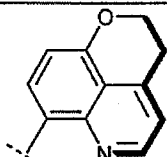
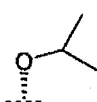
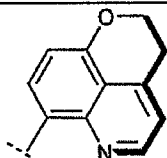
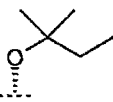
and

pharmaceutically acceptable salts or esters thereof.

21. The compound according to claim 1 having the following formula:



wherein R<sup>3</sup> and R<sup>4</sup> are defined as:

| R <sup>4</sup>                                                                      | R <sup>3</sup>                                                                       |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
|  |  |
|  |  |

and

pharmaceutically acceptable salts or esters thereof.

22. A compound of formula (I) according to any one of claims 1 to 21 or a pharmaceutically acceptable salt or ester thereof, as a medicament.
23. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 21 or a pharmaceutically acceptable salt or ester thereof; and one or more

pharmaceutically acceptable carriers.

24. The pharmaceutical composition according to claim 23 additionally comprising at least one other antiviral agent.
25. The pharmaceutical composition as defined in claim 24 wherein the at least one other antiviral agent comprises at least one NNRTI.
26. The pharmaceutical composition as defined in claim 24 wherein the at least one other antiviral agent comprises at least one NRTI.
27. The pharmaceutical composition as defined in claim 24 wherein the at least one other antiviral agent comprises at least one protease inhibitor.
28. The pharmaceutical composition as defined in claim 24 wherein the at least one other antiviral agent comprises at least one entry inhibitor.
29. The pharmaceutical composition as defined in claim 24 wherein the at least one other antiviral agent comprises at least one integrase inhibitor.
30. Use of a pharmaceutical composition according to any one of claims 23 to 29 for the treatment of an HIV infection in a mammal having or at risk of having the infection.
31. 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 21, a pharmaceutically acceptable salt or ester thereof, or a composition according to any one of 23 to 29.
32. 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 21 or a pharmaceutically acceptable salt or ester thereof, and at least one other antiviral agent; or a composition

according to any one of claims 23 to 29.

- 33. Use of a compound of formula (I) according to any one of claims 1 to 21, 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.
- 34. Use of a compound of formula (I) according to any one of claims 1 to 21, 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.
- 35. 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 21 or a pharmaceutically acceptable salt or ester thereof.
- 36. 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 21, or a salt or ester thereof, under conditions where replication of HIV is inhibited.
- 37. Use of a compound of formula (I) according to any one of claims 1 to 21 to inhibit the activity of the HIV integrase enzyme.
- 38. Use of a compound of formula (I) according to any one of claims 1 to 21, or a salt or ester thereof, to inhibit the replication of HIV.