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(54) **Title:**
INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION

(57) **Abstract:**
Compounds of formula I wherein a, R1, R2, R3, R4, R5 and R6 are defined herein, are useful as inhibitors of HIV replication.

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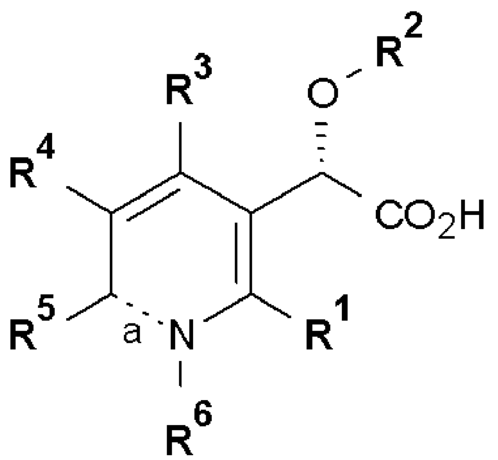
(54) Title: INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION



(I)

(57) **Abstract**: Compounds of formula I wherein a, R^1, R^2, R^3, R^4, R^5 and R^6 are defined herein, are useful as inhibitors of HIV replication.

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INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION

RELATED APPLICATIONS

This application claims benefit of U.S. Serial No. 61/178551, filed May 15, 2009, and U.S. Serial No. 61/285766, filed December 11, 2009, which are 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 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

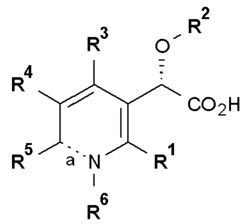
Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), particularly the HIV-1 strain. Most currently approved therapies for HIV infection target the viral reverse transcriptase and protease enzymes. There are also two approved drugs targeting HIV entry and one 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.

International patent application WO 2007/131350 and United States published patent application US 2006/0106070 describe compounds which are active against HIV replication.

SUMMARY OF THE INVENTION

The present invention provides a novel series of compounds having inhibitory activity against HIV replication. Therefore, the compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.

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



(I)

wherein

R[1] is (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{3-6})cycloalkyl, wherein the (C_{1-6})alkyl is optionally substituted with –O(C_{1-6})alkyl or -S(C_{1-6})alkyl;

R[2] is (C_{1-8})alkyl or (C_{3-8})cycloalkyl, wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl;

R[3] is aryl, wherein the aryl is optionally fused to one or more cycles, at least one of which is a heterocycle, to form a heteropolycycle, and wherein the aryl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and -O(C_{1-6})alkyl;

R[4] is (C_{1-6})alkyl, -CN, halo, (C_{1-6})haloalkyl, (C_{3-5})cycloalkyl, or –O(C_{1-6})alkyl; and

a is a double bond, **R**[6] is absent and **R**[5] is **R**[51] or -(C_{1-3})alkyl-**R**[51]; or

a is a single bond and **R**[5] and **R**[6] are joined, together with the atoms to which they are bonded, to form a 5-membered ring optionally having 1 to 3 further heteroatoms each independently selected from O, N and S, wherein the 5-membered ring is optionally substituted with 1 to 3 **R**[51] substituents;

wherein **R**[51] is in each case independently selected from **R**[52], -O**R**[53], -N(**R**[54])**R**[53], -C(=O)**R**[52], -C(=O)O**R**[53], -C(=O)N(**R**[54])**R**[53], -OC(=O)N(**R**[54])**R**[53], -N(**R**[54])C(=O)**R**[52], -N(**R**[54])C(=O)N(**R**[54])**R**[53] and -N(**R**[54])C(=O)O**R**[53]; wherein

R[52] is in each case independently selected from **R**[53], (C_{2-8})alkenyl and (C_{2-8})alkynyl,

R[53] is in each case independently selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, and

R[54] is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of **R**[52] and **R**[53] is optionally substituted with 1 to 3 substituents each independently selected from **R**[55], halo, -CN, -O**R**[56], -S**R**[56], -SO**R**[56], -SO_2**R**[56], -N(**R**[54])**R**[56], -N(**R**[54])C(=O)**R**[55], -N(**R**[54])C(=O)N(**R**[54])**R**[56], -N(**R**[54])C(=O)O**R**[56], -OC(=O)N(**R**[54])**R**[56], -C(=O)**R**[55], -C(=O)O**R**[56], and -CON(**R**[54])**R**[56], wherein

R^{55} is in each case independently selected from **R^{56}**, (C_{2-8})alkenyl and (C_{2-8})alkynyl, and

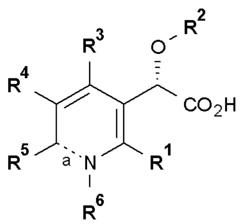
R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein each of **R^{55}** and **R^{56}** is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -OH, -O(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl, -N((C_{1-6})alkyl$)_2$ and -NH(C=O)(C_{1-6})alkyl;

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 thereof.

Another aspect of Formula (I) provides a compound of Formula II and a racemate, enantiomer or diastereomer of a compound of formula (II):



(II)

wherein

R^1 is (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{3-6})cycloalkyl, wherein the (C_{1-6})alkyl is optionally substituted with –O(C_{1-6})alkyl or -S(C_{1-6})alkyl;

R^2 is (C_{1-8})alkyl or (C_{3-8})cycloalkyl, wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl;

R^3 is aryl, wherein the aryl is optionally fused to one or more cycles, at least one of which is a heterocycle, to form a heteropolycycle, and wherein the aryl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and -O(C_{1-6})alkyl;

R^4 is (C_{1-6})alkyl, -CN, halo, (C_{1-6})haloalkyl, (C_{3-5})cycloalkyl, or –O(C_{1-6})alkyl; and

a is a double bond, **R^6** is absent and **R^5** is **R^{51}** or -(C_{1-3})alkyl-**R^{51}**; or

a is a single bond and $\mathbf{R}^5$ and $\mathbf{R}^6$ are joined, together with the atoms to which they are bonded, to form a 5-membered ring optionally having 1 to 3 further heteroatoms each independently selected from O, N and S, wherein the 5-membered ring is optionally substituted with 1 to 3 $\mathbf{R}^{51}$ substituents;

wherein $\mathbf{R}^{51}$ is in each case independently selected from $\mathbf{R}^{52}$, -O$\mathbf{R}^{53}$, -N($\mathbf{R}^{54}$)$\mathbf{R}^{53}$, -C(=O)$\mathbf{R}^{52}$, -C(=O)O$\mathbf{R}^{53}$, -C(=O)N($\mathbf{R}^{54}$)$\mathbf{R}^{53}$, -OC(=O)N($\mathbf{R}^{54}$)$\mathbf{R}^{53}$, -N($\mathbf{R}^{54}$)C(=O)$\mathbf{R}^{52}$, -N($\mathbf{R}^{54}$)C(=O)N($\mathbf{R}^{54}$)$\mathbf{R}^{53}$ and -N($\mathbf{R}^{54}$)C(=O)O$\mathbf{R}^{53}$; wherein

$\mathbf{R}^{52}$ is in each case independently selected from $\mathbf{R}^{53}$, (C_{2-8})alkenyl and (C_{2-8})alkynyl,

$\mathbf{R}^{53}$ is in each case independently selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{5-14})spirocycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, and

$\mathbf{R}^{54}$ is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of $\mathbf{R}^{52}$ and $\mathbf{R}^{53}$ is optionally substituted with 1 to 3 substituents each independently selected from $\mathbf{R}^{55}$, halo, -CN, -O$\mathbf{R}^{56}$, -S$\mathbf{R}^{56}$, -SO$\mathbf{R}^{56}$, -$SO_2$$\mathbf{R}^{56}$, -N($\mathbf{R}^{54}$)$\mathbf{R}^{56}$, -N($\mathbf{R}^{54}$)C(=O)$\mathbf{R}^{55}$, -N($\mathbf{R}^{54}$)C(=O)N($\mathbf{R}^{54}$)$\mathbf{R}^{56}$, -N($\mathbf{R}^{54}$)C(=O)O$\mathbf{R}^{56}$, -OC(=O)N($\mathbf{R}^{54}$)$\mathbf{R}^{56}$, -C(=O)$\mathbf{R}^{55}$, -C(=O)O$\mathbf{R}^{56}$, and -CON($\mathbf{R}^{54}$)$\mathbf{R}^{56}$, wherein

$\mathbf{R}^{55}$ is in each case independently selected from $\mathbf{R}^{56}$, (C_{2-8})alkenyl and (C_{2-8})alkynyl, and

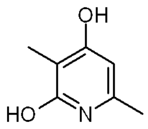
$\mathbf{R}^{56}$ is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein each of $\mathbf{R}^{55}$ and $\mathbf{R}^{56}$ is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -OH, -O(C_{1-6})alkyl, -NH_2, -NH(C_{1-6})alkyl, -N((C_{1-6})alkyl)$_2$ and -NH(C=O)(C_{1-6})alkyl;

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 thereof.

Another aspect of the invention provides one or more intermediates selected from the formulas: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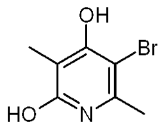
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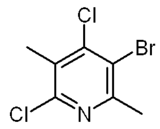
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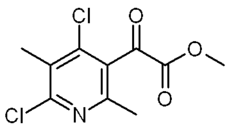
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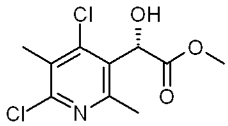
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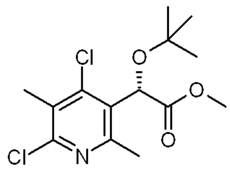
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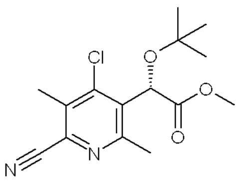
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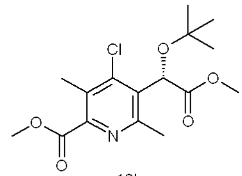
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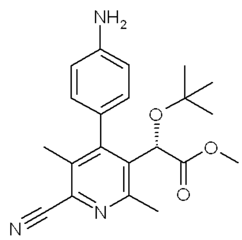
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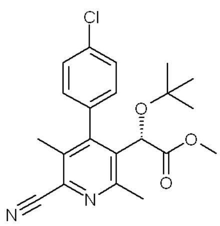
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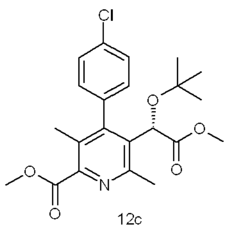
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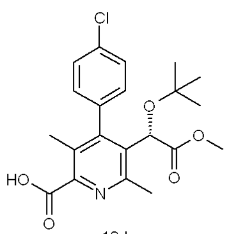
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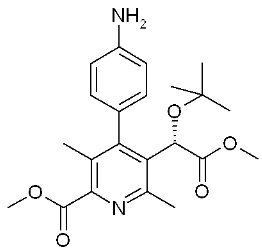
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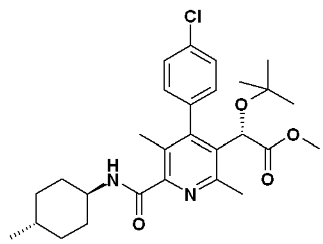

37a .

Another aspect of this invention provides a compound of formula (I) or a pharmaceutically acceptable salt 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 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 human being having or at risk of having the infection.

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

Another aspect of the invention involves a method of treating an HIV infection in a human being having or at risk of having the infection, the method comprising administering to the human being a therapeutically effective amount of a combination of a compound of formula (I) or a pharmaceutically acceptable salt 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 thereof, for the treatment of an HIV infection in a human being 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 thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being 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 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 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 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.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass salts, including pharmaceutically acceptable salts thereof and solvates thereof, such as for instance hydrates, including solvates of the free compounds or solvates of a salt of the compound. For example, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purpose of the present invention.

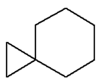
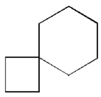
In one aspect the present invention also provides all pharmaceutically-acceptable isotopically labeled compounds of the present invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. Examples of isotopes suitable for inclusion in the compounds of the present invention include isotopes of hydrogen, for example 2H or 3H. Isotopically labeled compounds of the present invention, for example deuterated versions of the compounds, can be prepared by conventional techniques known to those skilled in the art or by synthetic processes analogous to those described in the present application using appropriate isotopically labeled reagents in place of the non-labeled reagent mentioned therein.

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

The term "(C_{2-n})alkenyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a double bond. Examples of (C_{2-6})alkenyl radicals include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl, and 1-butenyl. Unless specified otherwise, the term "(C_{2-n})alkenyl" is understood to encompass individual stereoisomers where possible, including but not limited to (*E*) and (*Z*) isomers, and mixtures thereof. When a (C_{2-n})alkenyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "(C_{2-n})alkynyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a triple bond. Examples of (C_{2-6})alkynyl radicals include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butynyl. When a (C_{2-n})alkynyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "(C_{3-m})cycloalkyl" as used herein, wherein m is an integer, either alone or in combination with another radical, is intended to mean a cycloalkyl substituent containing from 3 to m carbon atoms. Examples of (C_{3-7})cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "(C_{5-n})spirocycloalkyl", wherein n is an integer, either alone or in combination with another radical, denotes a cycloalkyl multi-ring system having two rings linked by one common atom. Examples of (C_{5-14})spirocycloalkyl radicals include, but are not limited to,  and .

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

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

The term “aryl-(C_{1-n})alkyl-” as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with an aryl radical as defined above. Examples of aryl-(C_{1-6})alkyl- include, but are not limited to, phenylmethyl (benzyl), 1-phenylethyl, 2-phenylethyl and phenylpropyl. When an aryl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the aryl or the alkyl portion thereof or both, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "**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 “**Het**-(C_{1-n})alkyl-” as used herein and unless specified otherwise, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a **Het** substituent as defined above. Examples of **Het**-(C_{1-6})alkyl- include, but are not limited to, thienylmethyl, furylmethyl, piperidinylethyl, 2-

pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, quinolinylpropyl, and the like. When an **Het**-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the **Het** or the alkyl portion thereof or both, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

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

The term “carbocycle” as used herein, either alone or in combination with another radical, is intended to mean a 3- to 8-membered saturated, unsaturated or aromatic cyclic radical in which all of the ring members are carbon atoms, and which may be fused to one or more 3- to 8-membered saturated, unsaturated or aromatic carbocyclic groups. When a 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 "heterocycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a 3- to 7-membered saturated, unsaturated or aromatic heterocycle containing from 1 to 4 heteroatoms each independently selected from O, N and S; or a monovalent radical derived by removal of a hydrogen atom therefrom. Examples of such heterocycles include, but are not limited to, azetidine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, thiazolidine, oxazolidine, pyrrole, thiophene, furan, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, tetrazole, piperidine, piperazine, azepine, diazepine, pyran, 1,4-dioxane, 4-morpholine, 4-thiomorpholine, pyridine, pyridine-N-oxide, pyridazine, pyrazine and pyrimidine, and saturated, unsaturated and aromatic derivatives thereof.

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

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

The term “(C_{1-n})haloalkyl” as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above wherein one or more hydrogen atoms are each replaced by a halo substituent. When two or more hydrogen atoms are replaced by halo substituents, the halo substituents may be the same or different. Examples of (C_{1-6})haloalkyl include but are not limited to chloromethyl, chloroethyl, dichloroethyl, bromomethyl, bromoethyl, dibromoethyl, chlorobromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl and difluoroethyl.

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

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

The term "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 designations and  are used interchangeably 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 phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include acetates, ascorbates, aspartates, benzenesulfonates, benzoates, besylates, bicarbonates, bitartrates, bromides/hydrobromides, Ca-edetates/edetates, camsylates, carbonates, chlorides/hydrochlorides, citrates, cyclamates, edisylates, ethane disulfonates, estolates, esylates, fumarates, gentisates (salt of 2,5-dihydroxy benzoic acid), gluceptates, gluconates, glutamates, glycinates, glycolates, glycollylarsnilates, hexylresorcinates, hydrabamines, hydroxymaleates, hydroxynaphthoates, iodides, isethionates, lactates, lactobionates, malates, maleates, malonates, mandelates, methanesulfonates, mesylates, methylbromides, methylnitrates, methylsulfates, mucates, napsylates, nitrates, oxalates, pamoates, pantothenates, phenylacetates, phosphates/diphosphates, polygalacturonates, propionates, saccharinates, salicylates, stearates subacetates, succinates, sulfamides, sulfates, tannates, tartrates, teoclates, toluenesulfonates, triethiodides, xinafoates (salt of 1-hydroxy-2-naphthoicacid) , ammonium, arginine, benzathines, chloroprocaines, cholines, diethanolamines, ethylenediamines, lysine, meglumines, TRIS (*C*,*C*,*C*-tris(hydroxymethyl)-aminomethan or Trometamol) and procaines. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19 and Handbook of Pharmaceutical Salts, P.Heinrich Stahl, Camille G. Wermuth (Eds.), Wiley-VCH, 2002, both of which are herein incorporated by reference).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention also comprise a part of the invention.

The term “treatment” as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term “treatment” also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life.

The term “antiviral agent” as used herein is intended to mean an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a human being, 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 human being.

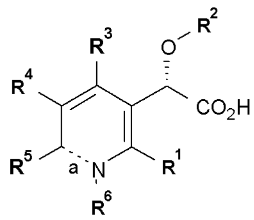
The term “inhibitor of HIV replication” as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro, ex vivo* or *in vivo*.

The term “HIV integrase” or “integrase”, used herein interchangeably, means the integrase enzyme encoded by the human immunodeficiency virus type 1. The polypeptide sequence of the integrase enzyme of NL4.3 strain of HIV-1 is provided as SEQ ID NO: 1.

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

PREFERRED EMBODIMENTS

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



(I)

according to this invention are described in detail. Any and each individual definition as set out herein may be combined with any and each individual definition as set out herein.

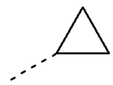
R^1:

R^1-A:

In at least one embodiment, **R^1** is (C_{1-4})alkyl, (C_{2-4})alkenyl or (C_{3-5})cycloalkyl, wherein the (C_{1-4})alkyl is optionally substituted with $-O(C_{1-3})$alkyl or $-S(C_{1-3})$alkyl.

R^1-B:

In at least one embodiment, **R^1** is selected from:

$-CH_3$, $-CH_2OMe$, $-CH_2OEt$, $-CH_2SMe$, $-CH=CH_2$ and  .

R^1-C:

In at least one embodiment, **R^1** is (C_{1-4})alkyl.

R^1-D:

In at least one embodiment, **R^1** is $-CH_3$.

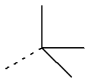
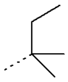
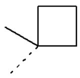
R^2:

R^2-A:

In at least one embodiment, **R^2** is (C_{3-8})alkyl or (C_{3-8})cycloalkyl wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl.

R^2-B:

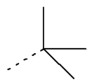
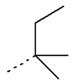
In at least one embodiment, **R^2** is selected from:

 ,  and  .

R^2-C:

In at least one embodiment, **R^2** is (C_{3-8})alkyl.

R^2-D:

In at least one embodiment, **R^2** is  or  .

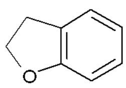
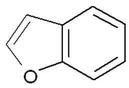
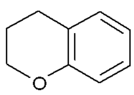
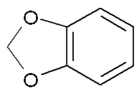
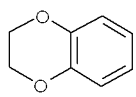
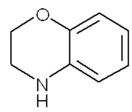
R^3:

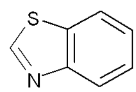
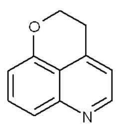
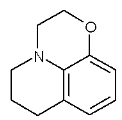
R^3-A:

In at least one embodiment, **R^3** is phenyl or **R^3** is phenyl fused to one or more cycles, at least one of which is a heterocycle, to form a 9- to 13-membered heteropolycycle having 1 or 2 heteroatoms, each independently selected from N, O and S; wherein the phenyl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and -O(C_{1-6})alkyl.

R^3-B:

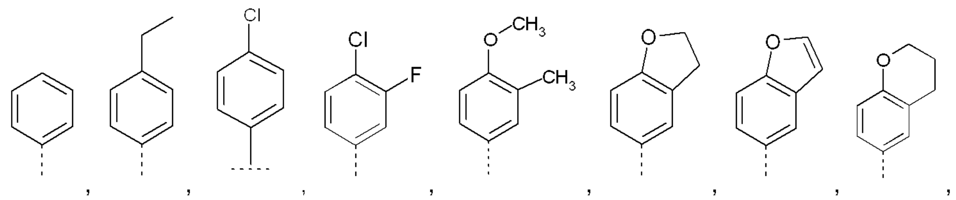
In at least one embodiment, **R^3** is phenyl or a heteropolycycle selected from:

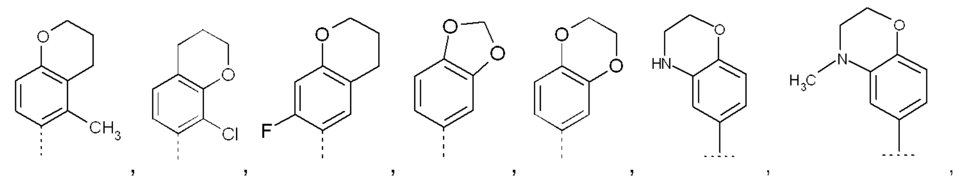
 ,  ,  ,  ,  ,  ,

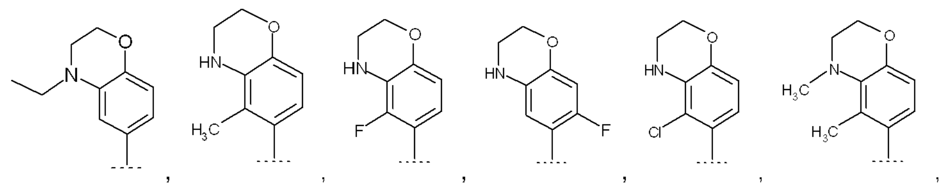
 ,  and  ; wherein the phenyl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and -O(C_{1-6})alkyl.

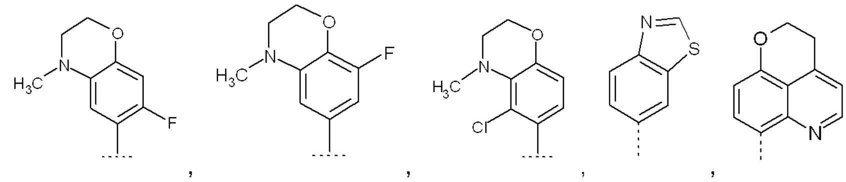
R³-C:

In at least one embodiment, **R³** is selected from:

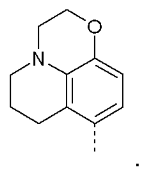






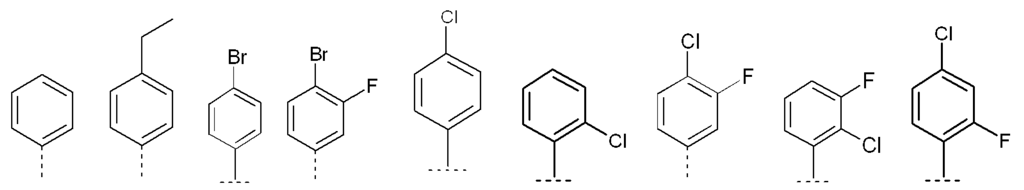


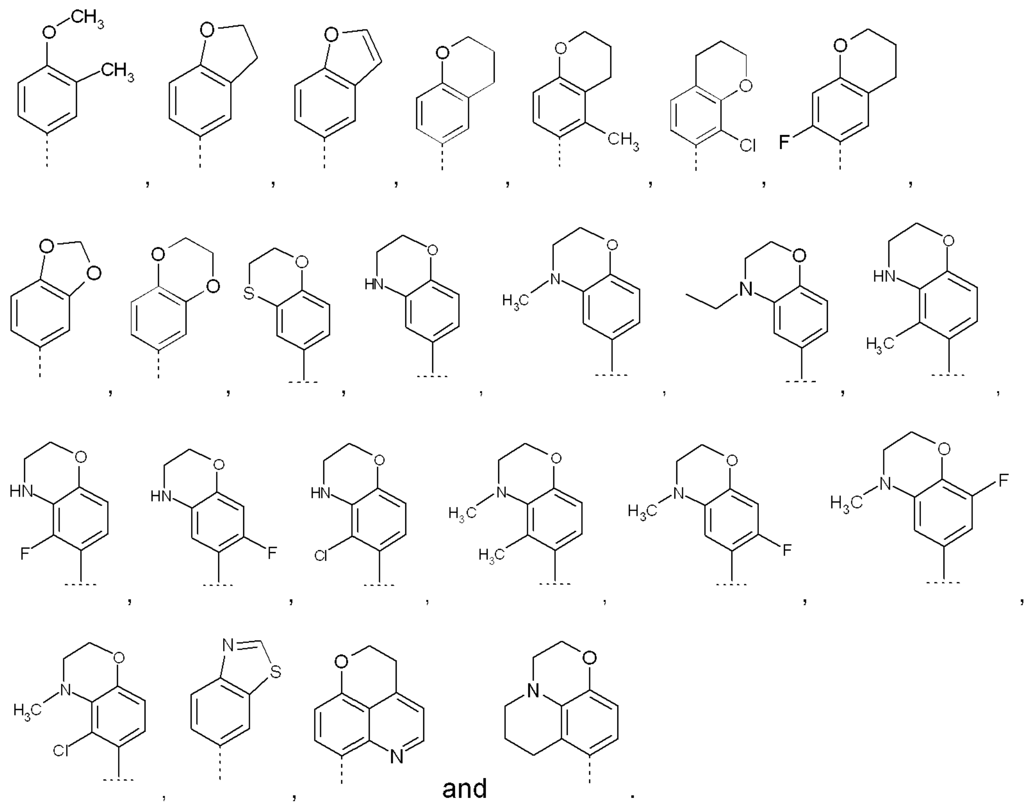
and



R³-D:

In at least one embodiment, **R³** is selected from:

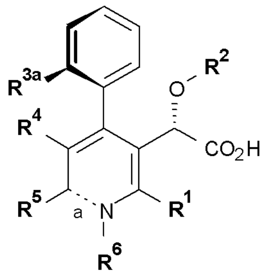




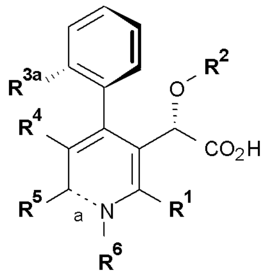
One skilled in the art will recognize that when the $\mathbf{R^3}$ substituent is not symmetrically substituted about the axis of rotation of the bond attaching $\mathbf{R^3}$ to **Core**, the compounds of the invention will have a rotational axis of asymmetry and thus rotational isomers are possible. When the energy barrier to rotation is relatively low, the rotational isomers rapidly interconvert at room temperature and are considered to be conformers. In contrast, when the energy barrier to rotation is relatively high, the rotational isomers interconvert so slowly at room temperature that they may be isolated and are considered to be atropisomers.

Because the compounds of the invention also posess at least one other chiral center, namely, the chiral carbon atom bonded to -O$\mathbf{R^2}$, the rotational isomers will exist as diastereomers. For example, when the unsymmetrically substituted $\mathbf{R^3}$ substituent bears a substituent $\mathbf{R^{3a}}$ at a position *ortho* to the bond attaching $\mathbf{R^3}$ to **Core**, wherein $\mathbf{R^{3a}}$ is any atom or group other than hydrogen which is a substituent of $\mathbf{R^3}$ by any definition of $\mathbf{R^3}$ set forth herein, the following atropisomeric formulas **A-**

1 and **A-2** are possible, where, in conformance with accepted stereochemical notation, the darkened and/or solid wedge bonds indicate the side or edge of the $\mathbf{R}^3$ substituent that is projecting towards the viewer:



A-1



A-2

Although for purposes of illustration, $\mathbf{R}^3$ is shown as phenyl unsymmetrically substituted at the ortho position with a substituent $\mathbf{R}^{3a}$ in formulas **A-1** and **A-2**, it will be clear to the person skilled in the art that analogous atropisomers exist for other unsymmetrically substituted $\mathbf{R}^3$ substituents.

It has been found that, when it is possible to separate the individual diastereomeric atropisomers so that their individual activities against HIV can be measured, the atropisomer with the formula similar to **A-1** above, where the substituent on the $\mathbf{R}^3$ group is on the opposite side of the plane of the pyridine ring from the –O$\mathbf{R}^2$ group, is in some cases more active against HIV, when measured, for example, by the procedure of Example 48 below, than the atropisomer with the formula similar to **A-2** above, where the substituent on the $\mathbf{R}^3$ group is on the same side of the plane of the pyridine ring as the –O$\mathbf{R}^2$ group.

$\mathbf{R}^4$:

$\mathbf{R}^4$-A:

In at least one embodiment, $\mathbf{R}^4$ is (C_{1-6})alkyl, -CN, halo or (C_{1-6})haloalkyl.

$\mathbf{R}^4$-B:

In at least one embodiment, $\mathbf{R}^4$ is (C_{1-6})alkyl, -CN or halo.

$\mathbf{R}^4$-C:

In at least one embodiment, $\mathbf{R}^4$ is selected from $-CH_3$, –CN and -F.

$\mathbf{R}^4$-D:

In at least one embodiment, $\mathbf{R}^4$ is (C_{1-6})alkyl.

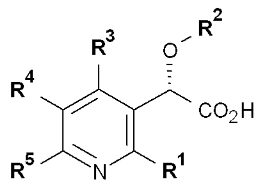
$\mathbf{R}^4$-E:

In at least one embodiment, $\mathbf{R}^4$ is $-CH_3$.

Core and R^5/R^6:

Core-A:

In at least one embodiment, **a** is a double bond and **R^6** is absent such that the compound of the invention is a compound of formula (Ia):



(Ia)

wherein **R^1**, **R^2**, **R^3**, **R^4** and **R^5** are as defined herein.

R^5/R^6-A:

In at least one embodiment, **a** is a double bond, **R^6** is absent and **R^5** is **R^{51}** or -(C_{1-3})alkyl-**R^{51}**;

wherein **R^{51}** is selected from **R^{52}**, -O**R^{53}**, -N(**R^{54}**)**R^{53}**, -C(=O)**R^{52}**, -C(=O)O**R^{53}**, -C(=O)N(**R^{54}**)**R^{53}**, -N(**R^{54}**)C(=O)**R^{52}**, -N(**R^{54}**)C(=O)N(**R^{54}**)**R^{53}** and -N(**R^{54}**)C(=O)O**R^{53}**; wherein

R^{52} is selected from **R^{53}** and (C_{2-8})alkenyl, and

R^{53} is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of **R^{52}** and **R^{53}** is optionally substituted with 1 to 3 substituents each independently selected from **R^{56}**, halo, -CN, -O**R^{56}**, -S**R^{56}**, -SO_2**R^{56}**, -N(**R^{54}**)**R^{56}** and -CON(**R^{54}**)**R^{56}**, wherein

R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **R^{56}** is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -O(C_{1-6})alkyl, -N((C_{1-6})alkyl)$_2$ and -NH(C=O)(C_{1-6})alkyl;

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.

R^5/R^6-B:

In at least one embodiment, **a** is a double bond, $\mathbf{R^6}$ is absent and $\mathbf{R^5}$ is $\mathbf{R^{51}}$ or -(C_{1-3})alkyl-$\mathbf{R^{51}}$;

wherein $\mathbf{R^{51}}$ is selected from $\mathbf{R^{52}}$, -O$\mathbf{R^{53}}$, -N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$, -C(=O)$\mathbf{R^{52}}$, --C(=O)O$\mathbf{R^{53}}$, -C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$, -N($\mathbf{R^{54}}$)C(=O)$\mathbf{R^{52}}$, -N($\mathbf{R^{54}}$)C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$ and -N($\mathbf{R^{54}}$)C(=O)O$\mathbf{R^{53}}$; wherein

$\mathbf{R^{52}}$ is selected from $\mathbf{R^{53}}$ and (C_{2-8})alkenyl, and

$\mathbf{R^{53}}$ is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from a 5- or 6-membered saturated, unsaturated or aromatic heterocycle having 1 to 3 heteroatoms each independently selected from O, N and S, and an 8- 9- or 10-membered saturated, unsaturated or aromatic heteropolycycle having 1 to 3 heteroatoms each independently selected from O, N and S; and

$\mathbf{R^{54}}$ is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of $\mathbf{R^{52}}$ and $\mathbf{R^{53}}$ is optionally substituted with 1 to 3 substituents each independently selected from $\mathbf{R^{56}}$, halo, -CN, -O$\mathbf{R^{56}}$, -S$\mathbf{R^{56}}$, -$SO_2$$\mathbf{R^{56}}$, -N($\mathbf{R^{54}}$)$\mathbf{R^{56}}$, and -CON($\mathbf{R^{54}}$)$\mathbf{R^{56}}$, wherein

$\mathbf{R^{56}}$ is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from a 5- or 6-membered saturated, unsaturated or aromatic heterocycle having 1 to 3 heteroatoms each independently selected from O, N and S;

wherein $\mathbf{R^{56}}$ is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -O(C_{1-6})alkyl, -N((C_{1-6})alkyl)$_2$ and -NH(C=O)(C_{1-6})alkyl.

$\mathbf{R^5/R^6}$-C:

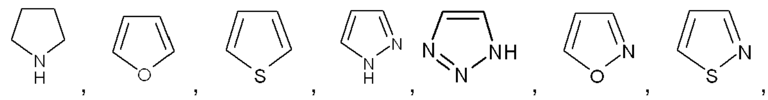
In at least one embodiment, **a** is a double bond, $\mathbf{R^6}$ is absent and $\mathbf{R^5}$ is $\mathbf{R^{51}}$ or -(C_{1-3})alkyl-$\mathbf{R^{51}}$;

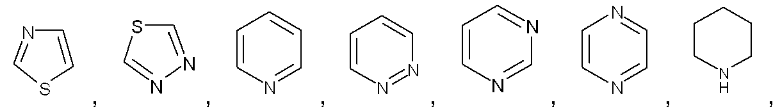
wherein $\mathbf{R^{51}}$ is selected from $\mathbf{R^{52}}$, -O$\mathbf{R^{53}}$, -N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$, -C(=O)$\mathbf{R^{52}}$, --C(=O)O$\mathbf{R^{53}}$, -C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$, -N($\mathbf{R^{54}}$)C(=O)$\mathbf{R^{52}}$, -N($\mathbf{R^{54}}$)C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$ and -N($\mathbf{R^{54}}$)C(=O)O$\mathbf{R^{53}}$; wherein

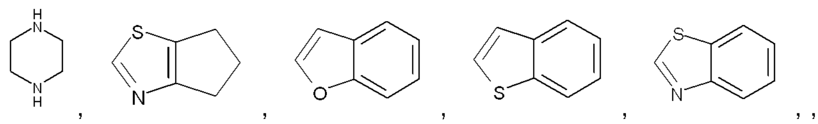
$\mathbf{R^{52}}$ is selected from $\mathbf{R^{53}}$ and (C_{2-8})alkenyl, and

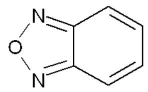
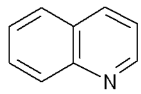
$\mathbf{R^{53}}$ is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:







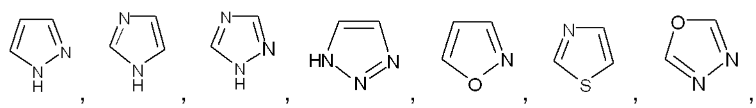
 and  ; and

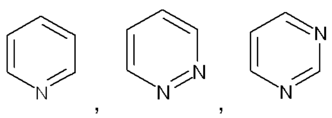
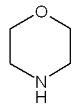
$\mathbf{R^{54}}$ is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of $\mathbf{R^{52}}$ and $\mathbf{R^{53}}$ is optionally substituted with 1 to 3 substituents each independently selected from $\mathbf{R^{56}}$, halo, -CN, -O$\mathbf{R^{56}}$, -S$\mathbf{R^{56}}$, -$SO_2$$\mathbf{R^{56}}$, -N($\mathbf{R^{54}}$)$\mathbf{R^{56}}$ and -CON($\mathbf{R^{54}}$)$\mathbf{R^{56}}$, wherein

$\mathbf{R^{56}}$ is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:

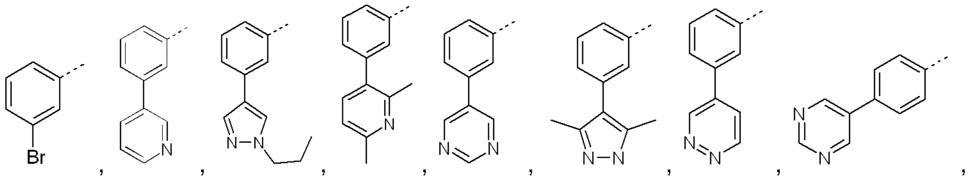


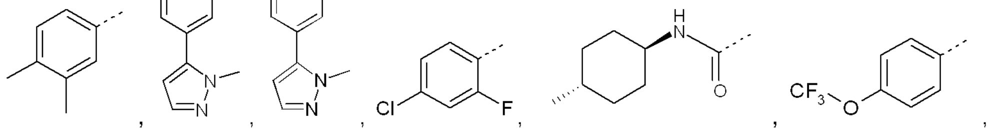
 and ;

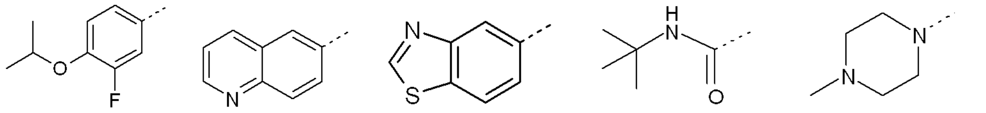
wherein $\mathbf{R^{56}}$ is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, $-O(C_{1-6})$alkyl, $-N((C_{1-6})alkyl)_2$ and $-NH(C{=}O)(C_{1-6})$alkyl.

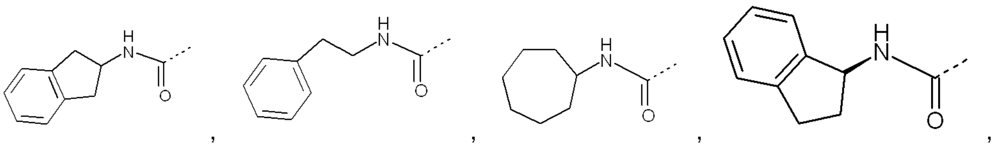
R^5/R^6-D:

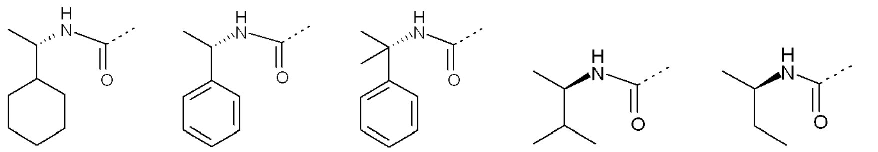
In at least one embodiment, **a** is a double bond, $\mathbf{R^6}$ is absent and $\mathbf{R^5}$ is selected from:

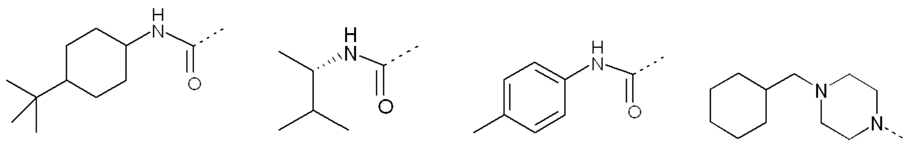


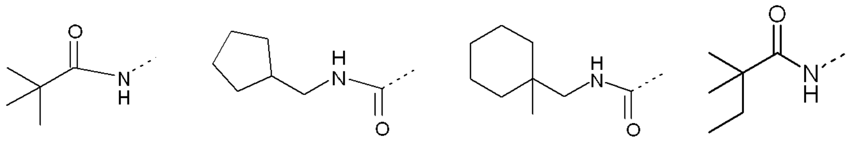


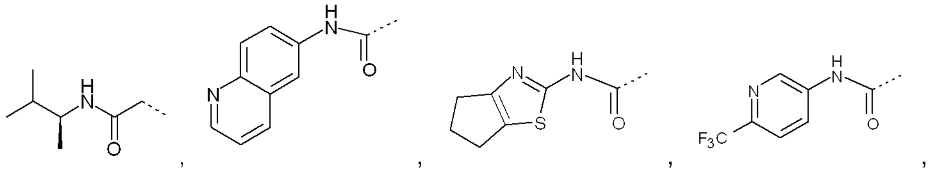


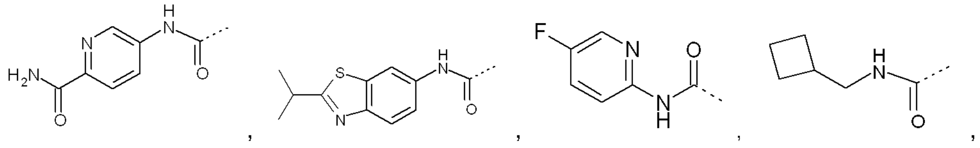


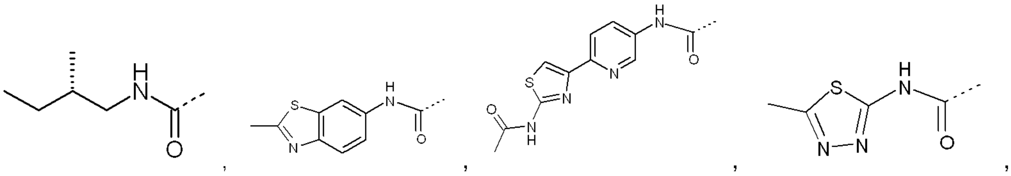


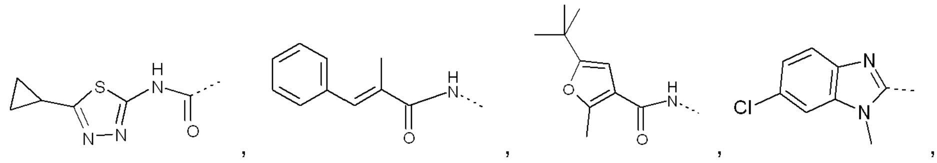


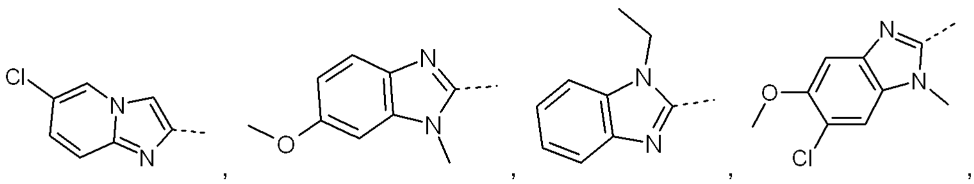


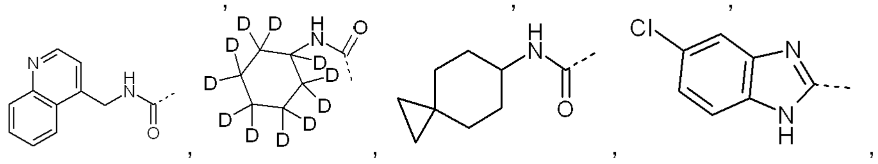


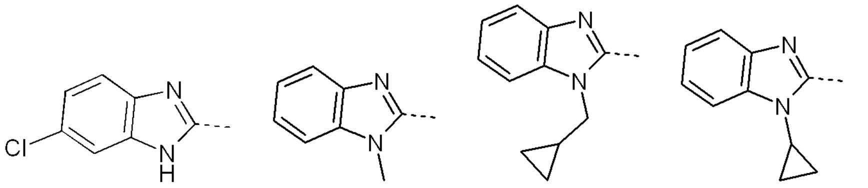


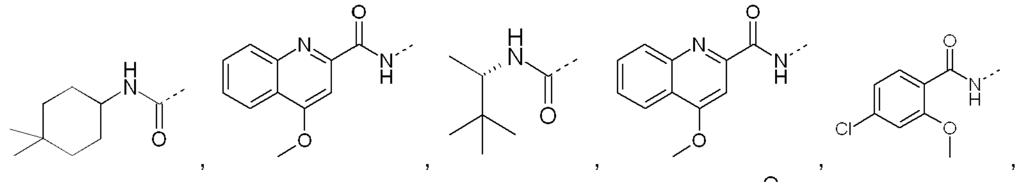


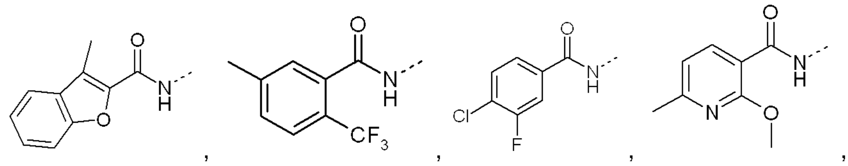


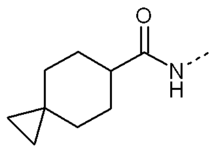
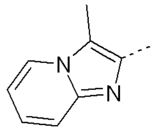
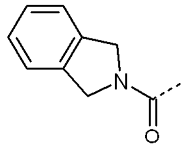










,  and .

R^5/R^6-E:

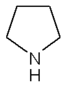
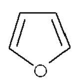
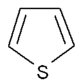
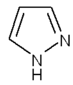
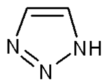
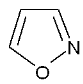
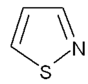
In at least one embodiment, **a** is a double bond, $\mathbf{R^6}$ is absent and $\mathbf{R^5}$ is $\mathbf{R^{51}}$ or -(C_{1-3})alkyl-$\mathbf{R^{51}}$;

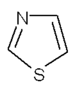
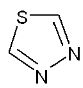
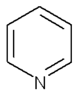
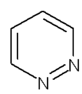
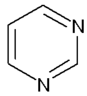
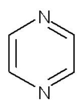
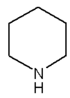
wherein $\mathbf{R^{51}}$ is selected from $\mathbf{R^{52}}$, -O$\mathbf{R^{53}}$, -C(=O)$\mathbf{R^{52}}$, --C(=O)O$\mathbf{R^{53}}$, -C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$, -N($\mathbf{R^{54}}$)C(=O)$\mathbf{R^{52}}$, -N($\mathbf{R^{54}}$)C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$ and -N($\mathbf{R^{54}}$)C(=O)O$\mathbf{R^{53}}$; wherein

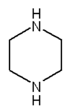
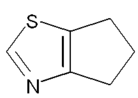
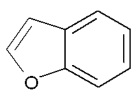
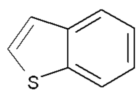
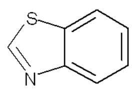
$\mathbf{R^{52}}$ is selected from $\mathbf{R^{53}}$ and (C_{2-8})alkenyl, and

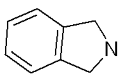
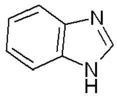
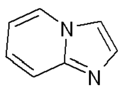
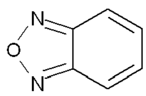
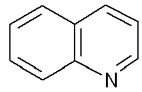
$\mathbf{R^{53}}$ is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:

, , , , , , ,

, , , , , , ,

, , , , ,

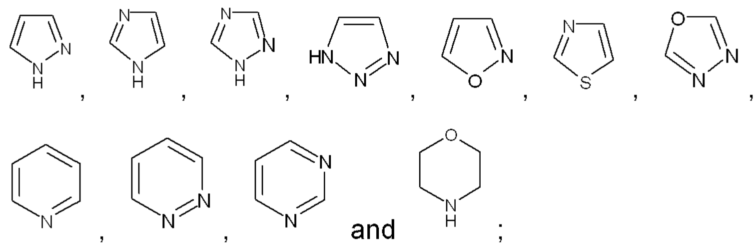
, , ,  and ;

and

$\mathbf{R^{54}}$ is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of $\mathbf{R^{52}}$ and $\mathbf{R^{53}}$ is optionally substituted with 1 to 3 substituents each independently selected from $\mathbf{R^{56}}$, halo, -CN, -O$\mathbf{R^{56}}$, -S$\mathbf{R^{56}}$, -$SO_2$$\mathbf{R^{56}}$, -N($\mathbf{R^{54}}$)$\mathbf{R^{56}}$ and -CON($\mathbf{R^{54}}$)$\mathbf{R^{56}}$, wherein

$\mathbf{R^{56}}$ is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



wherein $\mathbf{R^{56}}$ is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -O(C_{1-6})alkyl, -N((C_{1-6})alkyl)$_2$ and -NH(C=O)(C_{1-6})alkyl.

R^5/R^6-F:

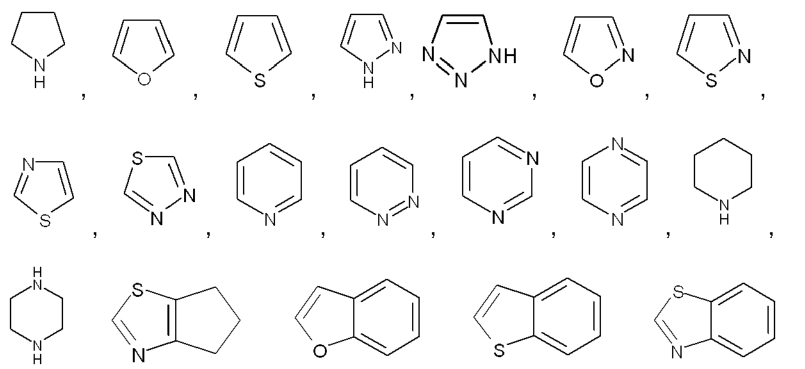
In at least one embodiment, **a** is a double bond, $\mathbf{R^6}$ is absent and $\mathbf{R^5}$ is $\mathbf{R^{51}}$ or -(C_{1-3})alkyl-$\mathbf{R^{51}}$;

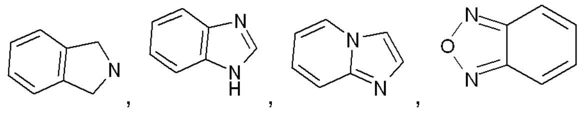
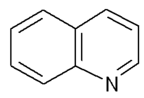
wherein $\mathbf{R^{51}}$ is selected from $\mathbf{R^{52}}$, -O$\mathbf{R^{53}}$, -C(=O)$\mathbf{R^{52}}$, --C(=O)O$\mathbf{R^{53}}$, -C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$, -N($\mathbf{R^{54}}$)C(=O)$\mathbf{R^{52}}$, -N($\mathbf{R^{54}}$)C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$ and -N($\mathbf{R^{54}}$)C(=O)O$\mathbf{R^{53}}$; wherein

$\mathbf{R^{52}}$ is selected from $\mathbf{R^{53}}$ and (C_{2-8})alkenyl, and

$\mathbf{R^{53}}$ is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{7-12})spirocycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



 and  ;

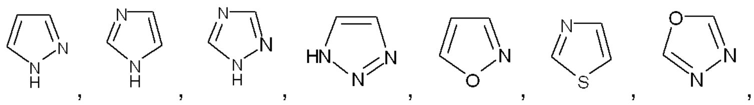
and

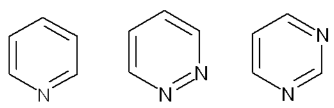
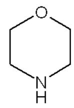
R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of **R**^{52} and **R**^{53} is optionally substituted with 1 to 3 substituents each independently selected from **R**^{56}, halo, -CN, -O**R**^{56}, -S**R**^{56}, $-SO_2$**R**^{56}, -N(**R**^{54})**R**^{56} and -CON(**R**^{54})**R**^{56}, wherein

R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



 and  ;

wherein **R**^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -O(C_{1-6})alkyl, -N((C_{1-6})alkyl$)_2$ and -NH(C=O)(C_{1-6})alkyl.

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^1	R^2	R^3	R^4	Core	R^5/R^6
E-1	R^1-A	R^2-A	R^3-A	R^4-A	Core-A	R^5/R^6-A
E-2	R^1-A	R^2-A	R^3-A	R^4-A	Core-A	R^5/R^6-B
E-3	R^1-A	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-A
E-4	R^1-A	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-B
E-5	R^1-A	R^2-A	R^3-A	R^4-D	Core-A	R^5/R^6-A
E-6	R^1-A	R^2-A	R^3-A	R^4-D	Core-A	R^5/R^6-B

Embodiment	R^1	R^2	R^3	R^4	Core	R^5/R^6
E-7	R^1-A	R^2-C	R^3-A	R^4-A	Core-A	R^5/R^6-A
E-8	R^1-A	R^2-C	R^3-A	R^4-A	Core-A	R^5/R^6-B
E-9	R^1-A	R^2-C	R^3-A	R^4-B	Core-A	R^5/R^6-A
E-10	R^1-A	R^2-C	R^3-A	R^4-B	Core-A	R^5/R^6-B
E-11	R^1-A	R^2-C	R^3-A	R^4-D	Core-A	R^5/R^6-A
E-12	R^1-A	R^2-C	R^3-A	R^4-D	Core-A	R^5/R^6-B
E-13	R^1-B	R^2-B	R^3-D	R^4-E	Core-A	R^5/R^6-C
E-14	R^1-B	R^2-B	R^3-D	R^4-E	Core-A	R^5/R^6-E
E-15	R^1-B	R^2-D	R^3-B	R^4-B	Core-A	R^5/R^6-D
E-16	R^1-B	R^2-A	R^3-B	R^4-D	Core-A	R^5/R^6-D
E-17	R^1-B	R^2-D	R^3-D	R^4-D	Core-A	R^5/R^6-A
E-18	R^1-C	R^2-A	R^3-A	R^4-A	Core-A	R^5/R^6-A
E-19	R^1-C	R^2-A	R^3-A	R^4-A	Core-A	R^5/R^6-B
E-20	R^1-C	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-A
E-21	R^1-C	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-B
E-22	R^1-C	R^2-A	R^3-A	R^4-D	Core-A	R^5/R^6-A
E-23	R^1-C	R^2-A	R^3-A	R^4-D	Core-A	R^5/R^6-B
E-24	R^1-C	R^2-C	R^3-A	R^4-A	Core-A	R^5/R^6-A
E-25	R^1-C	R^2-C	R^3-A	R^4-A	Core-A	R^5/R^6-B
E-26	R^1-C	R^2-C	R^3-A	R^4-B	Core-A	R^5/R^6-A
E-27	R^1-C	R^2-C	R^3-A	R^4-B	Core-A	R^5/R^6-B
E-28	R^1-C	R^2-C	R^3-A	R^4-D	Core-A	R^5/R^6-A
E-29	R^1-C	R^2-C	R^3-A	R^4-D	Core-A	R^5/R^6-B
E-30	R^1-C	R^2-B	R^3-B	R^4-A	Core-A	R^5/R^6-C
E-31	R^1-C	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-F
E-32	R^1-D	R^2-B	R^3-B	R^4-E	Core-A	R^5/R^6-C
E-33	R^1-D	R^2-D	R^3-C	R^4-E	Core-A	R^5/R^6-E
E-34	R^1-D	R^2-D	R^3-C	R^4-B	Core-A	R^5/R^6-E
E-35	R^1-D	R^2-B	R^3-C	R^4-B	Core-A	R^5/R^6-B
E-36	R^1-D	R^2-D	R^3-C	R^4-E	Core-A	R^5/R^6-F
E-37	R^1-D	R^2-D	R^3-C	R^4-B	Core-A	R^5/R^6-F

Examples of most preferred compounds according to this invention are each single compound listed in the following Tables 1 to 6.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers, and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers, atropisomers) resulting from all possible steriochemistry at a chiral center for which specific steriochemistry is not otherwise decsribed, and racemates thereof, as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist.

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 but not limited to differences in pharmacokinetic properties, including but not limited to metabolism, protein binding, and the like, and pharmacological properties, including but not limited to 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 but are not limited to 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. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, including but not limited to GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, including but not limited to CD, ORD, X-ray crystallography, or NMR.

PHARMACEUTICAL COMPOSITION

Suitable preparations for administering the compounds of the invention will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing one or more compounds according to the invention with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers.

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.

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 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 thereof.

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

The dose range of the compounds of the invention applicable per day is usually from 0.001 to 100 mg/kg of body weight, preferably from 0.01 to 50 mg/kg of body weight. Each dosage unit may conveniently contain from 5% to 95% active compound (w/w). Preferably such preparations contain from 20% to 80% active compound.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

When the composition of this invention comprises a combination of a compound of the invention and one or more additional therapeutic or prophylactic 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.

COMBINATION THERAPY

Combination therapy is contemplated wherein a compound according to the invention, or a pharmaceutically acceptable salt 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 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 human being, 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 human being. Such agents can be selected from:

- NRTIs (nucleoside or nucleotide reverse transcriptase inhibitors) including but not limited to zidovudine/RETROVIR® (GSK), didanosine/VIDEX® (BMS), stavudine/ZERIT® (BMS), lamivudine/EPIVIR® (GSK/Shire), emtricitabine/EMTRIVA® (Gilead Sciences), abacavir/ZIAGEN® (GSK), and tenofovir/VIREAD® (Gilead Sciences), apricitabine (Avexa), elvucitabine (Achillion) and OBP-601 (Oncolys), amdoxovir (RFS Pharma);
- NNRTIs (non-nucleoside reverse transcriptase inhibitors) including but not limited to nevirapine/VIRAMUNE® (Boehringer Ingelheim), delavirdine/RESCRIPTOR® (Pfizer), efavirenz/SUSTIVA® (BMS), etravirine/INTELENCE® (Johnson & Johnson), rilpivirine (Johnson & Johnson), UK-453,061 (Pfizer) and RDEA806 (Ardea Biosciences), IDX-899 (GSK);

- protease inhibitors including but not limited to ritonavir/NORVIR® (Abbott), tipranavir/APTIVUS® (Boehringer Ingelheim), saquinavir/INVIRASE® (Hoffmann LaRoche), nelfinavir/VIRACEPT® (Pfizer), indinavir/CRIXIVAN® (Merck), fosamprenavir/LEXIVA® (GSK/Vertex), atazanavir/REYATAZ® (BMS), lopinavir/KALETRA® (Abbott), and darunavir/PREZISTA® (Johnson & Johnson);
- entry inhibitors including but not limited to
    - CCR5 antagonists including but not limited to maraviroc/SELZENTRY® (Pfizer), vicriviroc (Schering-Plough), INCB9471 (Incyte), PF-232798 (Pfizer), PRO-140 (Progenics Pharm), GSK706769 (GSK), PF-232798 (Pfizer), TBR-220 and TBR-652 (Tovira Therapeutics);
    - CXCR4 antagonists including but not limited to AMD-11070 (Genzyme),
    - fusion inhibitors including but not limited to enfuvirtide/FUZEON® (Trimeris), sifuvirtide (Fasogen), albuvirtide (Frontier Bio), FRI-1144 (Trimeris); and
    - others including but not limited to BMS-488043 (BMS);
- integrase inhibitors including but not limited to raltegravir/ISENTRESS® (Merck), elvitegravir (Gilead Sciences), GSK1349572 and GSK1265744 (GSK), JTK-656 (Japan Tobacco);
- TAT inhibitors;
- maturation inhibitors including but not limited to bevirimat (Myriad Genetics), vivecon (Myriad Genetics); and
- immunomodulating agents including but not limited to levamisole/ERGAMISOL® (Janssen-Ortho); 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.

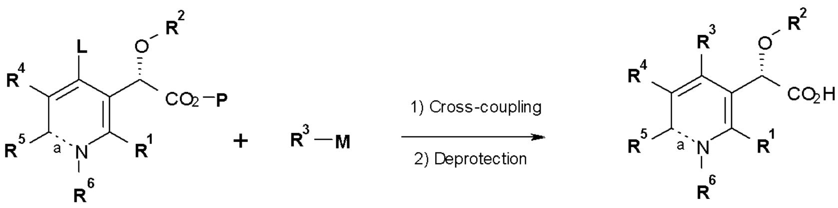
According to still another embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one entry inhibitor.

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

Methodology and Synthesis

The synthesis of compounds of formula (I) according to this invention is conveniently accomplished following the general procedures outlined in the schemes below wherein **a**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$ and $\mathbf{R^6}$ are as defined herein. Other procedures by which compounds of the invention may be prepared are well known in the art or are set forth in the examples below.

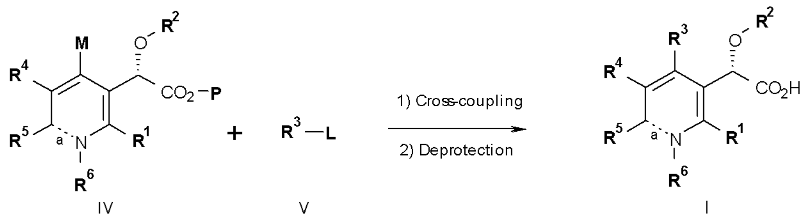
Scheme 1



Intermediates **II**, wherein **a**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^4}$, $\mathbf{R^5}$ and $\mathbf{R^6}$ are as defined herein, **L** is a leaving group including but not limited to iodo, bromo, chloro or -OTf, and **P** is a protecting group chosen from commonly used protecting groups for carboxylic acids, including but not limited to a methyl or ethyl ester, and intermediates **III**, wherein $\mathbf{R^3}$ is as defined herein and **M** is a group suitable for reacting with group **L** in a coupling reaction, such as are well known in the art, including but not limited to $-B(OH)_2$ or a boronate ester incuding but not limited to $-B(OCH_3)_2$ and $-B(OC(CH_3)_2C(CH_3)_2O)$; -I; $-Sn\mathbf{R}_3$ wherein **R** is (C_{1-6})alkyl; or -Zn**X** wherein **X** is halo, are commercially available or are prepared by reactions well known in the art or as set forth in the examples below. Protected derivatives of compounds of formula (I) can be prepared by well known coupling reactions of intermediates **II** and **III**, including but not limited to Suzuki cross-coupling between a boronic acid or boronate ester derivative **III** and a halo or triflate derivative **II**; copper catalyzed Ullmann cross-coupling between iodo derivatives **II** and **III**; Negishi cross-coupling between an arylzinc reagent **III** and an iodo or triflate derivative **II**; and Stille coupling between an aryltin reagent **III** and a bromo or iodo derivative **II**. The protected products of the coupling reaction are then deprotected, for example by saponification, to provide compounds of formula (I).

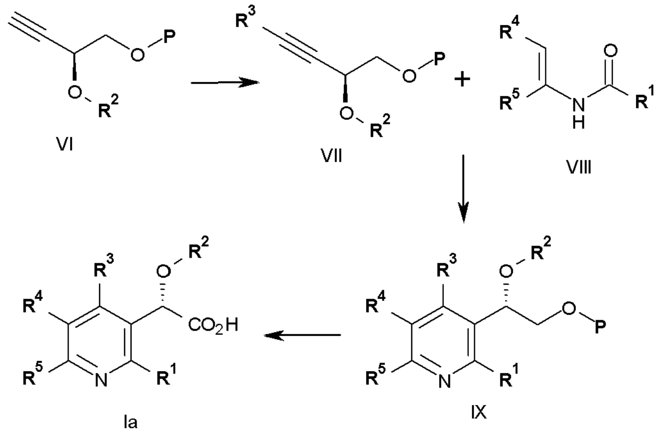
Alternatively, as shown in Scheme 2 below, intermediates **IV** and **V**, wherein **a**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, **L**, **M** and **P** are as defined herein, may be coupled using the cross-coupling methods described above, followed by deprotection, to provide compounds of formula (I).

Scheme 2



Furthermore, compounds of formula (Ia) wherein **a** is a single bond, $\mathbf{R^6}$ is absent and $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$ and $\mathbf{R^5}$ are as defined herein are conveniently prepared using the general procedure illustrated in Scheme 3 below.

Scheme 3



Intermediates **VI** and **VIII**, wherein **R**[1], **R**[2], **R**[3], **R**[4] and **R**[5] are as defined herein and **P** is a suitable protecting group, well known in the art, are commercially available or are prepared by reactions well known in the art or as set forth in the examples below. Intermediates **VI** are conveniently transformed to intermediates **VII** using conditions well-known to those skilled in the art, including but not limited to a Sonogashira coupling between intermediates **VI** and **R**[3]-I. Intermediates **VII** and **VIII** undergo a cyclocondensation reaction under well known conditions, including but not limited to reaction with $(CF_3SO_2)_2O$ (triflic anhydride) in the presence of 2-chloropyridine to give intermediates **IX**. Deprotection of intermediate **IX**, followed by oxidation of the primary alcohol using conditions well known in the art, including but not limited to oxidation with Dess-Martin periodinane followed by sodium chlorite oxidation, provides compounds of formula (Ia).

It will be apparent to one skilled in the art that a compound of formula (I), or any of the intermediates **II** to **XI** involved in its preparation, wherein any of the substituents **a**, **R**[1], **R**[2], **R**[3], **R**[4], **R**[5] and **R**[6] has one meaning as defined herein, may be transformed to another compound of formula (I), or to any of the intermediates **II** to **XI** involved in its preparation as appropriate, wherein any of the substituents **a**, **R**[1], **R**[2], **R**[3], **R**[4], **R**[5] and **R**[6] has a different meaning as defined herein, at any chemically convenient step in the preparation. Examples of such transformations include but are not limited to alkylation, conversion of an aromatic primary amino group to a chloro or bromo substituent using a Sandmeyer reaction, and reductive dehalogenation. In addition, the substituents **R**[1], **R**[2], **R**[3], **R**[4], **R**[5] and **R**[6] may be protected and/or deprotected at intermediate steps in the preparation of a compound of formula (I), as will be recognized by the skilled person.

Examples

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

As is well known to a person skilled in the art, reactions are performed in an inert atmosphere (including but not limited to nitrogen or argon) where necessary to protect reaction components from air or moisture. Temperatures are given in degrees Celsius (°C). Solution percentages and ratios express a volume to volume relationship, unless stated otherwise. Flash chromatography is carried out on silica gel (SiO2) 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 or RF 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 µm silica) or from Teledyne Isco (RediSep, 40-63 µm silica). Preparative HPLC is carried out under standard conditions using a SunFire™ Prep C18 OBD 5 µm 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.

Alternatively, preparative HPLC is carried out under standard conditions using a SunFire™ Prep C18 OBD 5 µm reverse phase column, 19 x 50 mm and a linear gradient employing 10 mM ammonium formate in H_2O (pH = 3.8); and MeOH. Alternatively, preparative HPLC is carried out under standard conditions using a XBridge™ Prep C18 OBD 5 µm reverse phase column, 19 x 50 mm and a linear gradient employing 10 mM ammonium bicarbonate in H_2O (pH = 10.0); and MeOH.

Analytical HPLC is carried out under standard conditions using a SunFire™ C18 (3.5 µm, 4.6x30 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	2.5	98	2
0.5	2.5	98	2
6.0	2.5	50	50
10.5	3.0	0	100
11.5	3.0	0	100

Alternatively, analytical HPLC is carried out under standard conditions using a SunFire™ C18 (3.5 µm, 4.6x30 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	2.5	98	2
0.6	2.5	98	2
5.5	2.5	50	50
7.3	3.0	0	100
7.9	3.0	0	100

Alternatively, analytical HPLC is carried out under standard conditions using a SunFire™ C18 (3.5 µm, 4.6x30 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	2.5	98	2
0.6	2.5	98	2
3.4	2.5	50	50
4.5	3.0	0	100
4.9	3.0	0	100

Alternatively, analytical HPLC is carried out under standard conditions using a SunFire™ C18 (3.5 μm, 4.6x30 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A 10 mM Ammonium Formate in H_2O (pH = 3.8); solvent B MeOH):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	4.0	98	2
2.85	4.0	0	100
2.86	5.0	0	100
3.60	5.0	0	100

Alternatively, analytical UPLC is carried out using a shorter run time using an Aquity™ HSST3 (1.8 μm, 2.1x50 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	0.9	98	2
1.5	0.9	50	50
2.6	0.9	0	100

Alternatively, analytical UPLC is carried out using a shorter run time using an Aquity™ HSST3 (1.8 μm, 2.1x50 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A 10 mM Ammonium Formate in H_2O (pH = 3.8); solvent B MeOH):

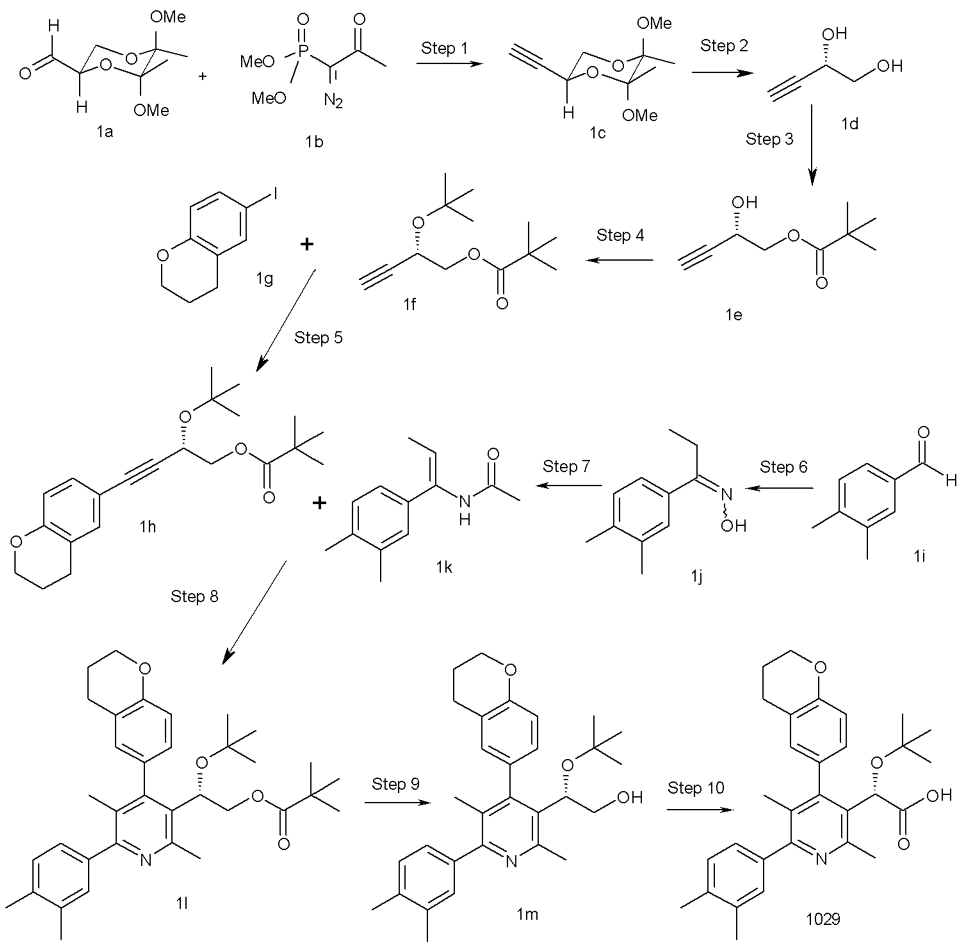
Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	0.8	95	5
2.30	0.9	0	100
2.32	1.0	0	100
3.00	1.0	0	100

Abbreviations or symbols used herein include:

Ac: acetyl; **AcOH**: acetic acid; **Ac_2O**: acetic anhydride; **BOC** or **Boc**: *tert*-butyloxycarbonyl; **BSA**: bovine serum albumin; **Bu**: butyl; **DABCO**: 1,4-diazabicyclo[2.2.2]octane; **DBU**: 1,8-diazabicyclo[5.4.0]undec-7-ene; **DCE**: dichloroethane; **DEAD**: diethyl azodicarboxylate; **DCM**: dichloromethane; **DIAD**: diisopropyl azodicarboxylate; **DIBAL**: diisobutyl aluminum hydride; **DMA**: dimethyl acetamide; **DMAP**: N,N-dimethyl-4-aminopyridine; **DME**: 1,2-dimethoxyethane; **DMF**: *N,N*-dimethylformamide; **DMSO**: dimethylsulfoxide; **DPPA**: diphenylphosphoryl azide; **Dppf**: 1,1'-Bis(diphenylphosphino)ferrocene; **EC_{50}**: 50% effective concentration;**eq**: equivalent; **Et**: ethyl; **Et_3N** : triethylamine; **Et_2O**: diethyl ether; **EtOAc**: ethyl acetate; **EtOH**: ethanol; **HPLC**: high performance liquid chromatography; **IC_{50}**: 50% inhibitory concentration; **^{i}Pr** or **i-Pr**: 1-methylethyl (*iso*-propyl); **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; **NMP**: N-methylpyrrolidone; **NMR**: nuclear magnetic resonance spectroscopy; **Ph**: phenyl; **PhMe**: toluene; **PG**: protecting group; **Pr**: propyl; **RPMI:** Roswell Park Memorial Institute (cell culture medium); **RT**: room temperature (approximately 18°C to 25°C); **SM**: starting material; **TBTU**: 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; ***tert*-butyl** or **t-butyl**: 1,1-dimethylethyl; **Tf**: trifluoromethanesulfonyl; **Tf_2O**: trifluoromethanesulfonic anhydride; **TFA**: trifluoroacetic acid; **THF**: tetrahydrofuran; **TLC**: thin layer chromatography; and **UPLC**: ultra high performance liquid chromatography.

EXAMPLE 1

SYNTHESIS OF COMPOUND 1029 (TABLE 1)



Step 1:

A mixture of aldehyde **1a** (5.85 g, 28.6 mmol; prepared according to Michel, P. and Ley, S. V. *Synthesis* **2003**, *10*, 1598-1602), phoshonate **1b** (6.6 g, 34 mmol) and K_2CO_3 (8.8 g, 64 mmol) in MeOH (125 mL) is stirred overnight at RT. The mixture is concentrated nearly to dryness and the residue is partitioned between H_2O (250 mL) and EtOAc (500 mL). The aqueous layer is washed with EtOAc (2 x 250 mL), and the combined organic layers are dried over anhydrous Na_2SO_4 and concentrated to give alkyne **1c**.

Step 2:

A mixture of alkyne **1c** (5.0 g, 25 mmol) in TFA (35 mL) and water (3.6 mL) is stirred at RT for about 30 min. The mixture is concentrated under reduced pressure and the residue is purified by CombiFlash® Companion to give diol **1d**.

Step 3:

A solution of diol **1d** (1.2 g, 14 mmol) and Et_3N (1.7 mL, 12 mmol) in DCM (80 mL) is cooled to 0°C under N_2. Trimethylacetyl chloride is added dropwise and the resulting mixture is allowed to stir overnight at RT. The reaction is quenched with MeOH (100 mL) and stirring is continued for about 20 min. The mixture is concentrated under reduced pressure and the residue is purified by CombiFlash® Companion to give the desired mono ester **1e**.

Step 4:

In a sealable reaction flask, a solution of the propargylic alcohol **1e** (375 mg, 2.20 mmol) and Amberlyst® H-15 resin (150 mg) in hexane (3 mL) is cooled to -78°C. Isobutene is then bubbled through the solution until the volume approximately doubles. The tube is then sealed, brought to RT and is stirred overnight. The tube is then cooled to -78°C, is opened and brought back to RT. The mixture is then filtered through a plug of SiO_2 (EtOAc wash) and concentrated under reduced pressure to provide pure *tert*-butyl ether **1f**.

Step 5:

Solid $Pd(PPh_3)_4$ (444 mg, 0.385 mmol) and CuI (146 mg, 0.769 mmol) are added successively to a mixture of **1g** (10 g, 34 mmol) and alkyne **1f** (11 g, 55 mmol) in DMF (23 mL) and Et_2NH (115 mL). The reaction mixture is stirred overnight at RT and then concentrated, diluted with EtOAc (300 mL) and washed successively with brine, 1 N aqueous HCl and water. The organic layer is dried over Na_2SO_4 and the residue purified by CombiFlash® Companion to give alkyne **1h**.

Step 6:

To a mixture of 3,4-dimethylbenzaldehyde (**1i**; 500 mg, 3.73 mmol) and Et_2O (12 mL) is added ethylmagnesium bromide (3M, 1.4 mL, 1.2 mmol) dropwise. After 15 min, the reaction is quenched with saturated aqueous NH_4Cl (50 mL) and the layers are separated. The organic layer is washed with saturated aqueous NH_4Cl (50 mL), dried over Na_2SO_4 and concentrated to give the intermediate benzyl alcohol. To a mixture of this material and DCM (28 mL) is added silica gel (2.2 g) followed by pyridinium chlorochromate (1.5 g, 7.2 mmol). The mixture is stirred for 45 min and the mixture is filtered through a plug of silica (3 x 1.5 cm) which is then washed with DCM (total of 50 mL). The filtrate is evaporated to dryness to give the intermediate ketone. This material is combined with sodium acetate (102 mg, 1.25 mmol) and hydroxylamine hydrochloride (87 mg, 1.25 mmol) in MeOH (0.8 mL) and is heated to 85ºC in a sealed tube. After 1 h, the reaction is allowed to cool to room temperature and concentrated onto silica gel (2 g). The product is purified by CombiFlash® Companion to give the oxime **1j** as a mixture of *cis*- and *trans*- isomers.

Step 7:

A mixture of oxime **1j** (130 mg, 0.73 mmol) and PhMe (1.7 mL) is degassed by bubbling N_2 gas through the solution for 30 min. Ph_3P (0.23 g, 0.88 mmol) is added and the mixture stirred for 10 min at RT. Ac_2O (84 µL, 0.89 mmol) is added and the mixture is stirred at reflux for 16 h, cooled to room temperature and concentrated *in vacuo*. A mixture of the residue, MeOH (3 mL) and excess K_2CO_3 (200 mg) is stirred for 1 h and the methanol is removed *in vacuo*. The residue is dissolved in EtOAc (10 mL) and water (5 mL). The organic layer is washed with water, concentrated and purified by CombiFlash® Companion to give amide **1k** as a mixture of *cis*- and *trans*- isomers.

Step 8:

Tf_2O (48 µL, 0.29 mmol) is added via syringe over 1 min to a stirred mixture of amide **1k** (55 mg, 0.27 mmol) and 2-chloropyridine (34 µL, 0.36 mmol) in DCM (0.7 mL) at -78ºC. After 5 min, the reaction flask is placed in an ice-water bath and warmed to 0ºC. Alkyne **1h** (69 mg, 0.19 mmol) in DCM (0.7 mL) is added *via* syringe and the mixture is allowed to warm to RT. After stirring for 30 min, Et_3N (1 mL) is added and the mixture is evaporated to dryness. The residue is dissolved in EtOAc (10 mL) and washed with water. The organic layer is dried over Na_2SO_4 and concentrated and the residue is purified by CombiFlash® Companion giving pyridine **1l**.

Step 9:

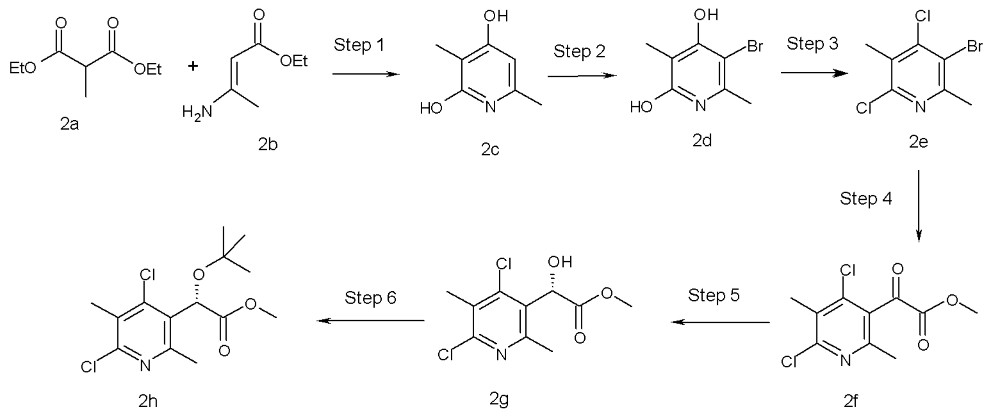
$LiBH_4$ in THF (2 M, 470 µL, 0.940 mmol) is added to a solution of ester **1l** (51 mg, 0.094 mmol) dissolved in THF (0.85 mL) and the reaction mixture is heated to 85°C and stirred for 30 min. Excess reagent is quenched with HCl (2 mL) and the mixture neutralized with $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give alcohol **1m**.

Step 10:

Dess-Martin periodinane (71 mg, 0.17 mmol) is added to a mixture of alcohol **1m** (43 mg, 0.094 mmol) and DCM (1.7 mL). After 2 h, the reaction mixture is concentrated, the residue is dissolved in 1:1 THF/tBuOH (2 mL), and 2,3-dimethyl-2-butene (1M in THF, 0.75 mL, 0.75 mmol) is added. A separate mixture of $NaClO_2$ (71 mg, 0.79 mmol) and NaH_2PO_4 (71 mg, 0.59 mmol) in water (1 mL) is added to the first mixture and the mixture is stirred at RT. After 30 min, the mixture is diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layer is dried over Na_2SO_4 and concentrated. The residue is purified by preparative HPLC to give compound **1029** (Table 1).

EXAMPLE 2

SYNTHESIS OF INTERMEDIATE 2H



Step 1:

To a solution of sodium ethoxide (1.48 L, 3.74 mol, 21% w/w in EtOH) at RT is added a solution of diethyl methylmalonate **2a** (645 mL, 3.72 mol) in anhydrous PhMe (330 mL). The resulting solution is stirred for 30 min and a solution of ethyl 3-aminocrotonate **2b** (485 mL, 3.71 mol) in anhydrous PhMe (490 mL) is added. The mixture is stirred at reflux for 39 h, EtOH (1-1.5 L) is removed by vacuum distillation, the mixture is cooled and water (1.6 L) is added. The mixture is stirred at 40°C for ~2 h, then is cooled and the phases are separated. The aqueous phase is washed with PhMe (2 x 50 mL) and then adjusted to pH 5-6 with conc. HCl. The solid is filtered and dried to afford dihydroxypyridine **2c**.

Step 2:

To a mixture of dihydroxypyridine **2c** (100 g, 0.718 mol) and DCM (800 mL) at ambient temperature is added dropwise Br_2 (37 mL, 150 g, 0.72 mol) in DCM (550 mL) over 16 min. The resulting mixture is stirred at RT for 1 h and intermediate **2d** is collected by filtration (HBr salt).

Step 3:

The bromopyridine **2d** (191 g, HBr salt) is heated at reflux in $POCl_3$ (850 mL) for 18 h and cooled to RT. The excess $POCl_3$ is removed by evaporation and the residue is poured onto ice. The mixture is adjusted to basic pH using 10 N NaOH and solid $NaHCO_3$. The mixture is filtered and the filtrate extracted with DCM (3 x 800 mL) and dried over Na_2SO_4. The solution is passed through a SiO_2 (600 g) column and concentrated to afford **2e**.

Alternative procedure for step 3:

Bromopyridine **2d** (370 g, HBr salt) is heated at reflux in $POCl_3$ (1.25 L) for 18 h. The mixture is cooled and excess $POCl_3$ is evaporated. To the residue is added $PhPOCl_2$ (1.2 L) and the mixture is heated at 150°C for 28 h. The mixture is allowed to cool to RT and poured onto ice, then adjusted to basic pH with solid Na_2CO_3. The mixture is filtered and the filtrate is extracted with EtOAc (3 x 1500 mL), dried over Na_2SO_4 and filtered. The filtrate is passed through a SiO_2 (600 g) column and concentrated, and the residue is triturated with EtOAc to give **2e** (196 g). The filtrate is concentrated and purified by CombiFlash® Companion to give a second crop of **2e**.

Step 4:

To a solution of bromide **2e** (105 g, 0.411 mol) in anhydrous THF (1.14 L) is added Cu(I)Br (15 g, 0.1 mol). To the resulting mixture at RT is added iPrMgCl-LiCl (400 mL, 0.52 mol, 1.3 M in THF) over 30 min. The mixture is allowed to stir for 1 h, methyl chlorooxoacetate (80 mL, 0.87 mol) is added and stirring is continued for 1 h. The reaction is quenched with saturated $NaHCO_3$ and solid $NaHCO_3$ and the mixture extracted with EtOAc (3 x 1.2 L). The organic extract is dried over Na_2SO_4, and filtered. The extract is passed through a SiO_2 (300 g) column, concentrated and the residue is purified by CombiFlash® Companion (EtOAc/ hexanes) to afford **2f**.

Step 5:

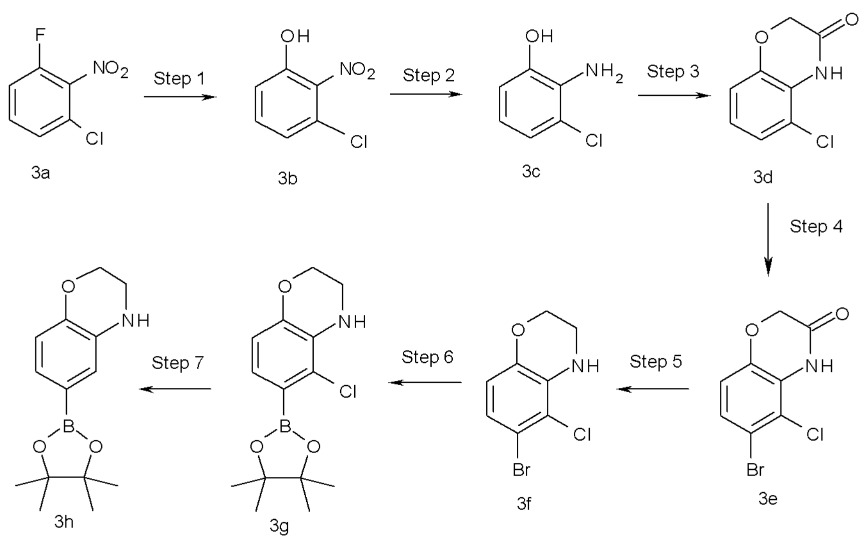
To a mixture of ester **2f** (65 g, 0.248 mol) in anhydrous PhMe (400 mL) in a 3 necked 5 L round bottom flask equipped with a magnetic stir bar, addition funnel, thermometer and gas-inlet is added (R)-2-methyl-CBS-oxazoborolidine (1 M solution in toluene, 50 mL, 50 mmol) with stirring. The mixture is cooled to -35°C and a solution of catecholoborane (36 mL, 40.5 g, 338 mmol) in toluene (240 mL) is added over a 2 h period. Stirring is continued at -35°C for 30 min. The mixture is allowed to warm to -15°C and is diluted with EtOAc (400 mL) and aqueous Na_2CO_3 (15 wt %, 800 mL). The mixture is stirred vigorously for 30 min, and the organic phase is separated and washed with aqueous Na_2CO_3 (15 wt %, 2 x 200 mL; vigorous stirring for 30 min each time) and aqueous NH_4Cl (15 wt %, 2 x 300 mL; vigorous stirring for 30 min each time). The organic layer is separated, passed through SiO_2 (300 g) eluting with EtOAc, and concentrated *in vacuo*. The residue is purified by CombiFlash® Companion to afford **2g**.

Step 6:

A mixture of **2g** (33.8 g, 0.128 mol) and t-butyl acetate (2.4 L) is cooled in an ice bath, and perchloric acid (70% aq) (300 mL) is added quickly. The flask is sealed and allowed to stir for 6 h at ~0-5°C. The reaction is quenched with a saturated solution of Na_2CO_3 (850 mL) and the mixture is adjusted to pH 8 -9 with solid Na_2CO_3. The mixture is filtered, the organic layer is separated and the aqueous layer extracted with EtOAc (3 x 750 mL), dried over Na_2SO_4, filtered and concentrated. DCM is added to the residue and the mixture is filtered. The organic phase is concentrated and purified using the CombiFlash® Companion (hexane/EtOAc: 1% to 30%) to afford **2h** (>98% ee by chiral HPLC) and recovered starting material **2g**.

EXAMPLE 3

SYNTHESIS OF INTERMEDIATES 3G AND 3H



Step 1:

To a mixture of 2-chloro-6-fluoronitrobenzene **3a** (6.62 g, 37.7 mmol) and $LiOH{\cdot}H_2O$

(6.33 g, 151 mmol) in THF (45 mL) and water (65 mL) is added aqueous H_2O_2 (30%, 8.6 mL, 80.0 mmol). The mixture is sealed and is heated to 60°C with rapid stirring. After 3 days, the mixture is cooled, added to half-saturated aqueous sodium thiosulfate (200 mL) and shaken vigorously in a separatory funnel. The mixture is acidified to pH < 3 with 1 N HCl, extracted with EtOAc (500 mL) and washed with brine (400 mL). The combined extracts are dried over magnesium sulfate, filtered and evaporated to give phenol **3b**.

Step 2:

To a mixture of phenol **3b** (6.37 g, 36.7 mmol) and THF (100 mL) is added tin powder (17.4 g, 147 mmol) followed by 1 N HCl (220 mL, 220 mmol) and the mixture is stirred vigorously at RT for 16 h. The mixture is cooled to 0°C and neutralized with 10 N NaOH (22 mL), and stirred vigorously for about 15 min. The mixture is filtered through a pad of Celite® and the solids are washed thoroughly with EtOAc (4 x 200 mL). The filtrate is acidified with 1 N HCl (4 mL) and diluted with brine (400 mL) and the organic phase is washed with brine (400 mL). The extract is dried over sodium sulfate, filtered and concentrated to afford aminophenol **3c**.

Step 3:

Chloroacetyl chloride (1.94 mL, 24.3 mmol) is added to an ice-cold mixture of aminophenol **3c** (2.91 g, 20.3 mmol) and K_2CO_3 (8.40 g, 60.8 mmol) in anhydrous DMF (200 mL) under a N_2 atmosphere. After 5 min, the reaction is allowed to warm to RT and, after a further 45 min, is heated to 50°C. After 15 h, the reaction is cooled and extracted with EtOAc (600 mL), and washed with water/brine (1 L), half-saturated sodium bicarbonate (1 L) and brine (600 mL). The organic phase is then dried over $MgSO_4$, filtered and concentrated to afford lactam **3d**.

Step 4:

Bromine (1.8 mL, 35 mmol) is slowly added dropwise to a stirred mixture of lactam **3d** (3.15 g; 17.1 mmol) in anhydrous DCM (40 mL) at RT. After 3 h, the mixture is slowly added to saturated aqueous sodium thiosulfate (200 mL) and extracted with DCM (4 x 100 mL). The combined extracts are washed with brine (200 mL), dried over $MgSO_4$, filtered and evaporated to afford the bromide **3e**.

Step 5:

A solution of borane in THF (1.0 M, 18.5 mL, 18.5 mmol) is added dropwise to an ice-cold mixture of lactam **3e** (4.00 g, 15.2 mmol) in anhydrous THF (75 mL), and the reaction is allowed to warm to RT. After about 30 min, the solution is heated to gentle reflux under a N_2 atmosphere. After 2 h, the mixture is cooled to 0°C, carefully quenched with 1N NaOH (19 mL) and stirred for about 15 min. The mixture is diluted with water (30 mL) and the THF is evaporated. The aqueous residue is 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 **3f**.

Step 6:

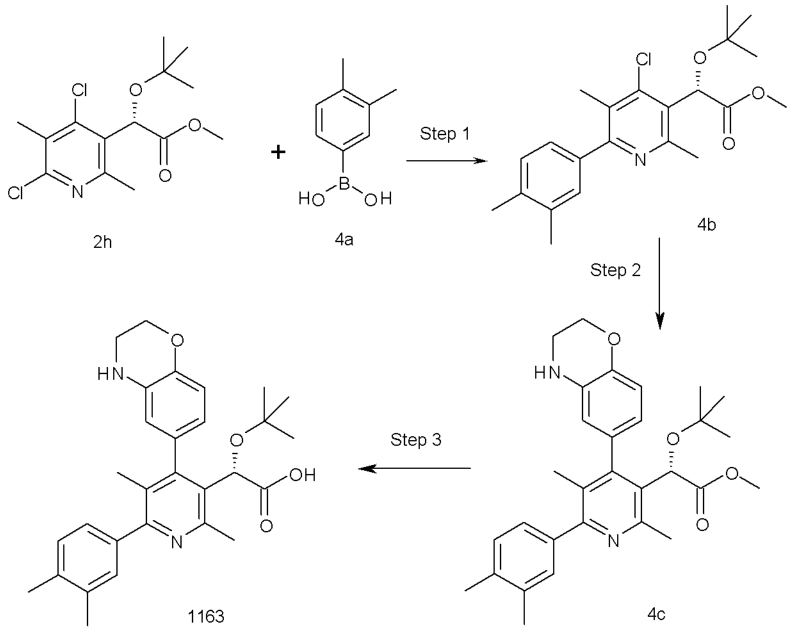
Anhydrous DMF (30 mL) is added to a flask charged with aryl bromide **3f** (1.84 g, 7.42 mmol), *bis*(pinacolato)diborane (2.83 g, 11.1 mmol) and potassium acetate (2.47 g, 26.0 mmol) and the mixture is deoxygenated by bubbling a stream of N_2 gas through the mixture for about 15 min. 1,1'-bis(diphenylphosphino)ferrocene (909 mg, 1.11 mmol) is added, and the mixture is deoxygenated for about a further 5 min and then heated to 95°C. After about 16 h, the reaction mixture is cooled, extracted with EtOAc (300 mL) and the extract is washed with 1:1 water/brine (500 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by chromatography over silica gel (EtOAc/hexanes) to afford the boronate **3g** contaminated with 0.8 eq of the diboron reagent.

Step 7:

Palladium on activated charcoal (10% Pd by weight, 1.08 g) is added to a mixture of aryl chloride **3g** (3.0 g, 10 mmol) and ammonium formate (6.4 g, 0.10 mol) in MeOH (75 mL). The mixture is heated at reflux for 30 min, cooled to RT and filtered through Celite®. The filter cake is rinsed with MeOH, the filtrate is concentrated to dryness and the residue is partitioned between water (50 mL) and EtOAc (100 mL). The organic layer is washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated to obtain boronic ester **3h**.

EXAMPLE 4

SYNTHESIS OF COMPOUND 1163 (TABLE 1)



Step 1:

To a solution of the dichloropyridine **2h** (Example 2) (2.0 g, 6.25 mmol) and 3,4-dimethylphenylboronic acid **4a** (1.12 g, 7.5 mmol) in DMF (20 mL) is added 2M Na_2CO_3 (7.8 mL, 16 mmol) followed by $PdCl_2(PPh_3)_2$ (440 mg, 0.62 mmol). The reaction mixture is degassed by bubbling with argon (10 min), the reaction vessel is sealed and the mixture is heated at 110°C for 16 h. The cooled mixture is diluted with EtOAc, washed with water and brine, dried over $MgSO_4$ and filtered. The residue is purified by CombiFlash® Companion (Hexanes/EtOAc) to give **4b**.

Step 2:

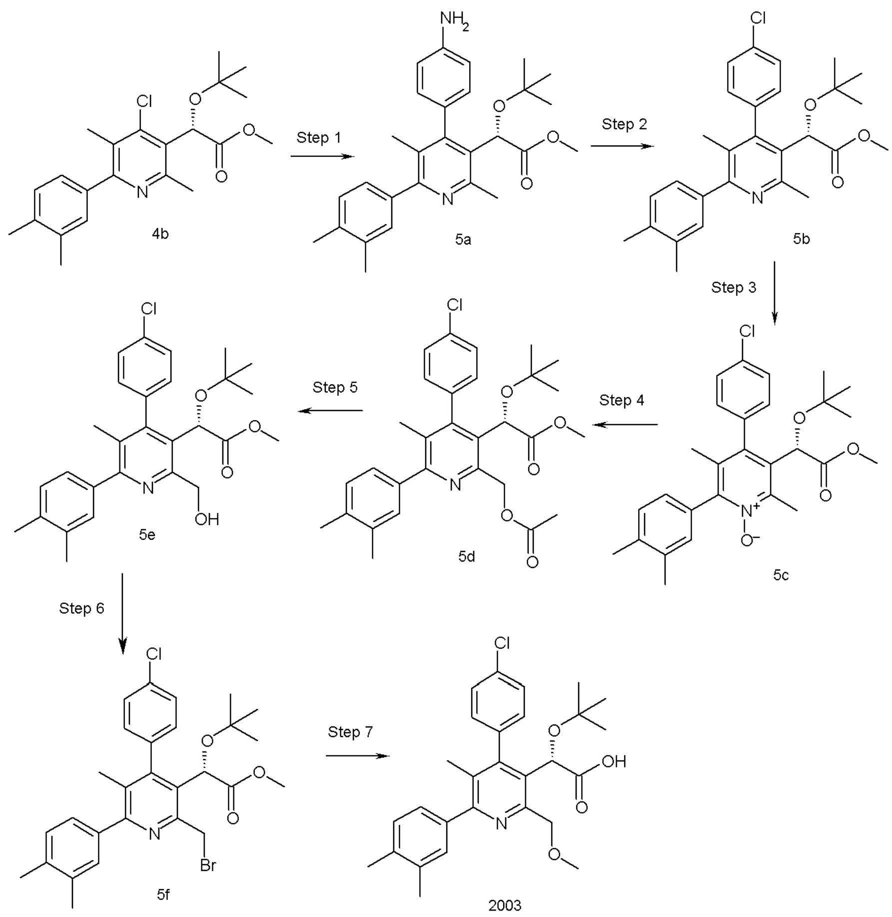
To a mixture of chloropyridine **4b** (250 mg, 0.64 mmol) in DMA (5.6 mL) is added boronate ester **3h** (Example 3) (218 mg, 0.83 mmol), $Pd([P(t\text{-}Bu)_3]_2$ (33 mg, 0.064 mmol), and $NaHCO_3$ (269 mg, 3.2 mmol), followed by water (565 μL). The mixture is degassed by bubbling with argon under sonication for 10 min, the reaction vessel is sealed and the mixture is heated at 130°C for 16 h. The reaction mixture is diluted with EtOAc (30 mL) and washed with brine (2x), water, and brine, dried over $MgSO_4$, filtered and concentrated and the residue is purified by CombiFlash® Companion (30% EtOAc/hexanes) to afford **4c**.

Step 3:

To a mixture of ester **4c** (191 mg, 0.39 mmol) and THF (8 mL)/MeOH (4 mL) is added 1.0N NaOH (4 mL, 4.0 mmol) at RT. The mixture is stirred at 50°C for 18 h, cooled to RT, quenched with AcOH and diluted with EtOAc. The mixture is washed with water and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue is purified by CombiFlash® Companion (DCM/MeOH, 0-5%) and the product is diluted with MeCN/H_2O, frozen and lyophilized to give compound **1163** (Table 1).

EXAMPLE 5

SYNTHESIS OF COMPOUND 2003 (TABLE 2)



Step 1:

To a solution of chloropyridine **4b** (Example 4) (2.0 g, 5.1 mmol) in DMA (40 mL) is added 4-(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)aniline (1.6 g; 7.2 mmol) followed by $NaHCO_3$ (2.2 g, 26 mmol) and distilled water (3 mL). The mixture is split into two microwave flasks and streams of argon gas are bubbled through the vigorously stirred mixtures for 30 min. *bis*-(Tri-*tert*-butylphosphine) palladium(0) catalyst (131 mg; 0.256 mmol) is added to each flask and the argon bubbling is continued for 10 min. The flasks are sealed and heated at 130°C for 16 h. The two reaction mixtures are pooled together, diluted with EtOAc (300 mL), and washed with water/brine (1:1 v/v; 5 x 100 mL) and brine (2 x 100 mL). The organic phase is dried over $MgSO_4$, filtered and concentrated. The residue is purified with CombiFlash® Companion to yield intermediate **5a**.

Step 2:

To a mixture of copper (II) chloride (558 mg, 4.15 mmol) and dry MeCN (20 mL) at 0°C under nitrogen atmosphere is added, dropwise, *t*-butyl nitrite (0.55 mL; 4.17 mmol). A solution of aniline **5a** (1.3 g, 2.9 mmol) in dry MeCN (20 mL) is added dropwise over 5 min and the ice bath removed after 15 min. After 16 h, the solvent is evaporated and the residue is adsorbed onto silica gel, purified by CombiFlash® Companion and dried under high vacuum to afford intermediate **5b**.

Step 3:

Meta-chloroperbenzoic acid (80%, 455 mg, 2.11 mmol) is added to a stirred mixture of pyridine **5b** (546 mg, 1.17 mmol) in anhydrous DCM (10 mL) and the reaction is allowed to stir at ambient temperature. After 2 days, additional *meta*-chloroperbenzoic acid (200 mg) and DCM (2 mL) are added and the stirring continued. After an additional day, the mixture is extracted with EtOAc (2 x 50 mL), and washed with saturated $NaHCO_3$ and brine. The combined organic phases are dried over $MgSO_4$ and concentrated to afford the N-oxide **5c**.

Step 4:

Pyridine N-oxide **5c** (1.17 mmol) is dissolved in Ac_2O (7.5 mL, 79 mmol) and the resulting solution is heated to 60°C under a nitrogen atmosphere. After 2 h, the solution is concentrated under high vacuum and the residue is dried under high vacuum for 1 h. The residue is extracted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ and brine. The extract is dried over $MgSO_4$ and concentrated to afford intermediate **5d**.

Step 5:

HCl in dioxane (4N; 1.0 mL, 4.0 mmol) is added to a stirred mixture of **5d** (1.17 mmol) and dry MeOH (4.2 mL) cooled to 0°C, and the mixture is allowed to warm to ambient temperature. After 21 h, the mixture is extracted with EtOAc (80 + 20 mL) and washed with saturated $NaHCO_3$ and brine. The combined extracts are dried over $MgSO_4$ and evaporated to afford alcohol **5e**.

Step 6:

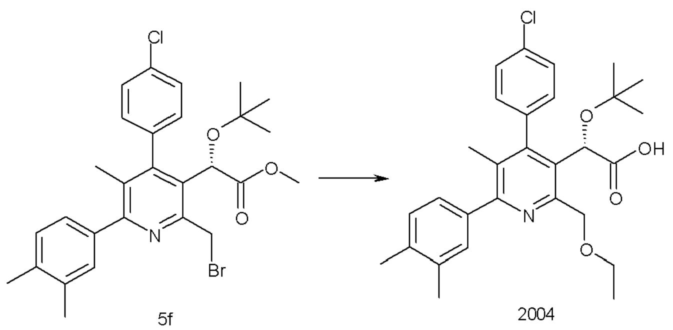
To a stirred mixture of alcohol **5e** (1.17 mmol) and anhydrous DCM (8 mL) at ambient temperature is added CBr_4 (427 mg, 1.3 mmol) followed by triphenylphosphine (339 mg; 1.3 mmol). The mixture is stirred at ambient temperature for 16 h, then diluted with DCM, absorbed onto silica gel and purified by CombiFlash® Companion to afford bromide **5f**.

Step 7:

NaH (60 % oil dispersion; *ca.* 2 mg) is added to a mixture of bromide **5f** (30 mg, 0.055 mmol), anhydrous THF (0.5 mL) and anhydrous MeOH (50 µL, 1.2 mmol) and the mixture is stirred in a sealed vial at ambient temperature. After 2 h, additional NaH (*ca.* 2 mg) is added and the stirring continued. After 17 h, the reaction mixture is acidified with acetic acid, diluted with water, filtered through a Millex filter, divided into two portions and purified by preparatory HPLC. The relevant fractions are pooled and lyophilized to afford compound **2003** (Table 2, TFA salt).

EXAMPLE 6

SYNTHESIS OF COMPOUND 2004 (TABLE 2)

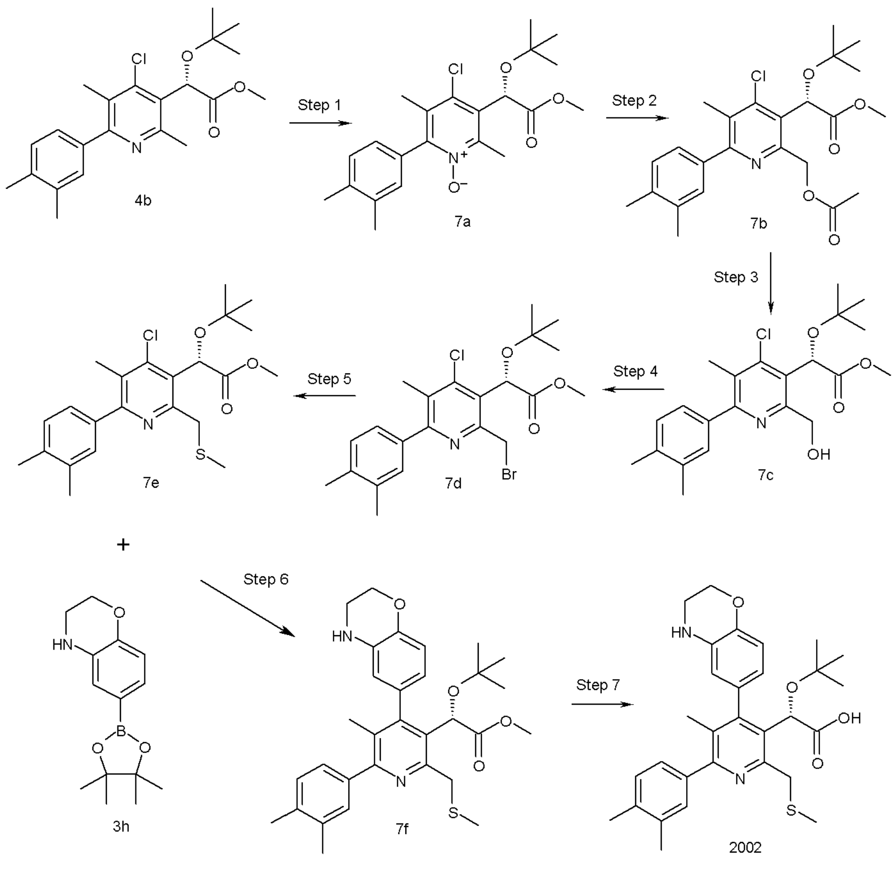


5f 2004

Intermediate **5f** (Example 5) is transformed to compound **2004** (Table 2) using the procedure described in step 7 of Example 5, except that MeOH is replaced with absolute EtOH.

EXAMPLE 7

SYNTHESIS OF COMPOUND 2002 (TABLE 2)



Step 1 to Step 4:

Intermediate **4b** (Example 4) is transformed to intermediate **7d** using the procedures described in steps 3 to 6 of Example 5.

Step 5:

To a stirred solution of bromide **7d** (314 mg, 0.67 mmol) in anhydrous DMF (2.0 mL) at ambient temperature is added sodium thiomethoxide (57 mg, 0.81 mmol). Stirring is continued for 1 h and the solution is extracted with EtOAc (75 mL) and washed with saturated $NaHCO_3$ and brine. The extract is dried over $MgSO_4$ and concentrated and the residue is purified by CombiFlash®Companion to afford the thioether **7e**.

Step 6:

To a mixture of chloropyridine **7e** (63 mg, 0.14 mmol), boronate ester **3h** (Example 3) (53 mg, 0.20 mmol), *bis*-(tri-*tert*-butylphosphine) palladium(0) catalyst (16 mg;

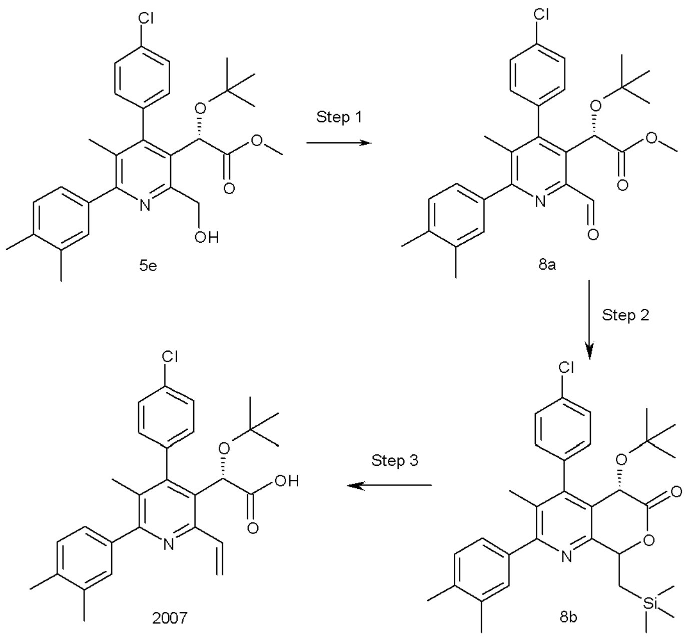
0.031 mmol), Dave-Phos ligand (24 mg, 0.061 mmol) and $NaHCO_3$ (60 mg, 0.71 mmol) in DMA (1.3 mL) in a microwave vial is added distilled water (0.13 mL), and the mixture is deoxygenated by bubbling argon for 15 min. The vial is sealed and heated to 130°C. After 16 h, the mixture is extracted with EtOAc (40 mL) and washed with water and brine. The extract is dried over $MgSO_4$ and concentrated, and the residue is purified by CombiFlash®Companion to afford intermediate **7f**.

Step 7:

To a mixture of ester **7f** (15 mg, 0.028 mmol) and $LiOH{\cdot}H_2O$ (10 mg, 0.24 mmol) is added THF (0.70 mL) followed by distilled water (0.15 mL) and MeOH (0.1 mL), and the mixture is heated to 45°C. After 16 h, the mixture is acidified with AcOH, diluted with MeCN / water, split into two portions and purified by preparatory HPLC. The relevant fractions are pooled and lyophilized to yield compound **2002** (Table 2) (TFA salt).

EXAMPLE 8

SYNTHESIS OF COMPOUND 2007 (TABLE 2)



Step 1:

A mixture of alcohol **5e** (Example 5) (200 mg, 0.49 mmol), Dess-Martin periodinane (251 mg; 0.59 mmol) and anhydrous DCM (6 mL) is stirred at RT under a nitrogen atmosphere for 18 h. The reaction mixture is vigorously stirred with saturated

$NaHCO_3$ / $Na_2S_2O_3$ (1:1, v/v, 12 mL) for 20 min and is extracted with DCM. The combined extracts are washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to afford the aldehyde **8a**.

Step 2:

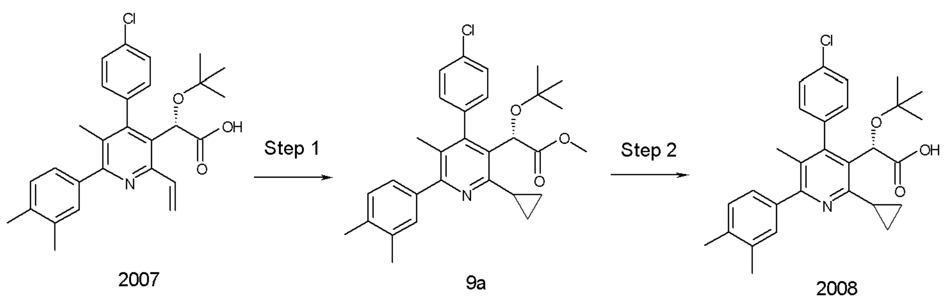
Trimethylsilylmethylmagnesium bromide (90%, 1M solution in Et_2O, 0.34 mL, 0.31 mmol) is added dropwise to a stirred solution of aldehyde **8a** (125 mg, 0.26 mmol) in anhydrous THF (2.0 mL) cooled to -35°C under a nitrogen atmosphere. After 1 h, additional trimethylsilylmethyl magnesium bromide solution (0.26 mL; 0.23 mmol) is added. After a further 2 h, the reaction is quenched with saturated NH_4Cl (1 mL) and the mixture is extracted with EtOAc (20 mL), and washed with 5% $NaHCO_3$ and brine. The extract is dried over $MgSO_4$, filtered and evaporated and the residue is purified by CombiFlash® Companion to afford lactone **8b**.

Step 3:

To a stirred mixture of lactone **8b** (98 mg; 0.183 mmol) and anhydrous THF (3.0 mL) under a nitrogen atmosphere is added dropwise tetrabutylammonium fluoride solution (1 M solution in THF; 0.27 mL; 0.27 mmol). The mixture is allowed to stir at 0°C for 30 min, then is allowed to warm to ambient temperature. After 1 h, the reaction is concentrated to dryness and the residue is dissolved in MeCN (10 mL). An aliquot (1 mL) is set aside and the remaining solution is adsorbed onto silica gel and purified by CombiFlash® to afford compound **2007** (Table 2). The 1 ml aliquot is purified by preparatory HPLC to yield compound **2007** (Table 2) (TFA salt).

EXAMPLE 9

SYNTHESIS OF COMPOUND 2008 (TABLE 2)



Step 1:

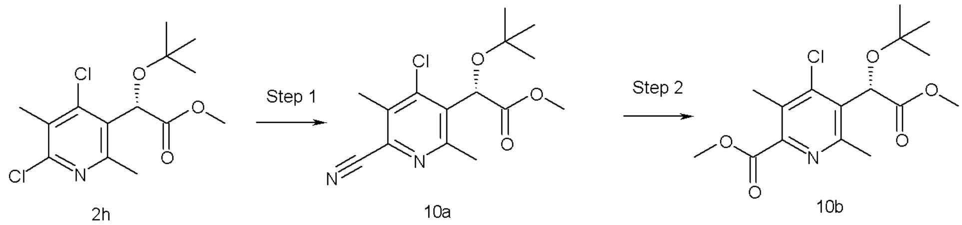
To a stirred, ice cold solution of compound **2007** (Example 8) (12 mg, 0.026 mmol) is added dropwise a solution of diazomethane in Et_2O (ca. 0.7 M, 2 mL) *via* a plastic pipette. After 5 min, palladium(II) acetate (5 mg, 0.02 mmol) is added and the mixture is stirred for 15 min. Nitrogen gas is bubbled through the solution to remove excess diazomethane and the residue is dried under high vacuum for 10 min to yield intermediate **9a**.

Step 2:

Intermediate **9a** is converted to compound **2008** using the procedure described in step 7 of Example 7.

EXAMPLE 10

SYNTHESIS OF INTERMEDIATE 10B



2h 10a 10b

Step 1:

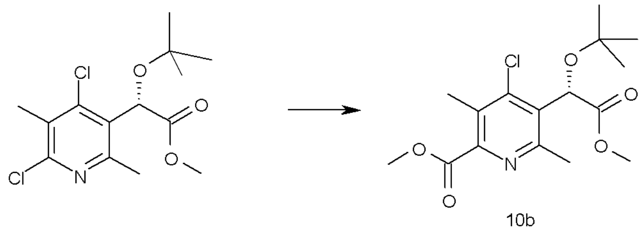
Dichloropyridine **2h** (Example 2) (11 g, 33 mmol), $Zn(CN)_2$ (7.8 g, 66 mmol) and $Pd[PPh_3]_4$ (1.9 g, 1.6 mmol) are combined in DMA (100 mL) and heated in a sealed tube to 115ºC. After 6 h, the reaction is cooled to RT, $Pd[PPh_3]_4$ (1.9 g, 1.6 mmol) is added and the reaction allowed to continue for 1 h. The mixture is cooled to RT, diluted with EtOAc (250 mL) and washed with water (250 mL). The aqueous layer is washed with EtOAc (100 mL) and the combined organic layers are washed with water (250 mL). The organic layer is dried over Na_2SO_4 and concentrated. The residue is purified by CombiFlash® Companion to give **10a**.

Step 2:

A mixture of nitrile **10a** (1.0 g, 3.2 mmol), aqueous NaOH (10 N, 3.4 mL, 32 mmol) and EtOH (3.2 mL) is heated at 90ºC in a sealed tube for 16 h. The mixture is cooled to RT and diluted with concentrated aqueous HCl (12N, 4 mL, 48 mmol) and water (50 mL). The mixture is extracted with EtOAc (3 x 50 mL) and the combined organic layers are dried over Na_2SO_4 and concentrated to dryness. The residue is taken up in MeOH (1 mL) and Et_2O (10 mL) and treated slowly with a hexane solution of $TMSCH_2N_2$ (2M, 3.5 mL, 7.0 mmol), and the mixture stirred for 10 min. The mixture is evaporated to dryness and the product is purified by CombiFlash® Companion to give the diester **10b**.

EXAMPLE 11

ALTERNATIVE SYNTHESIS OF INTERMEDIATE 10B

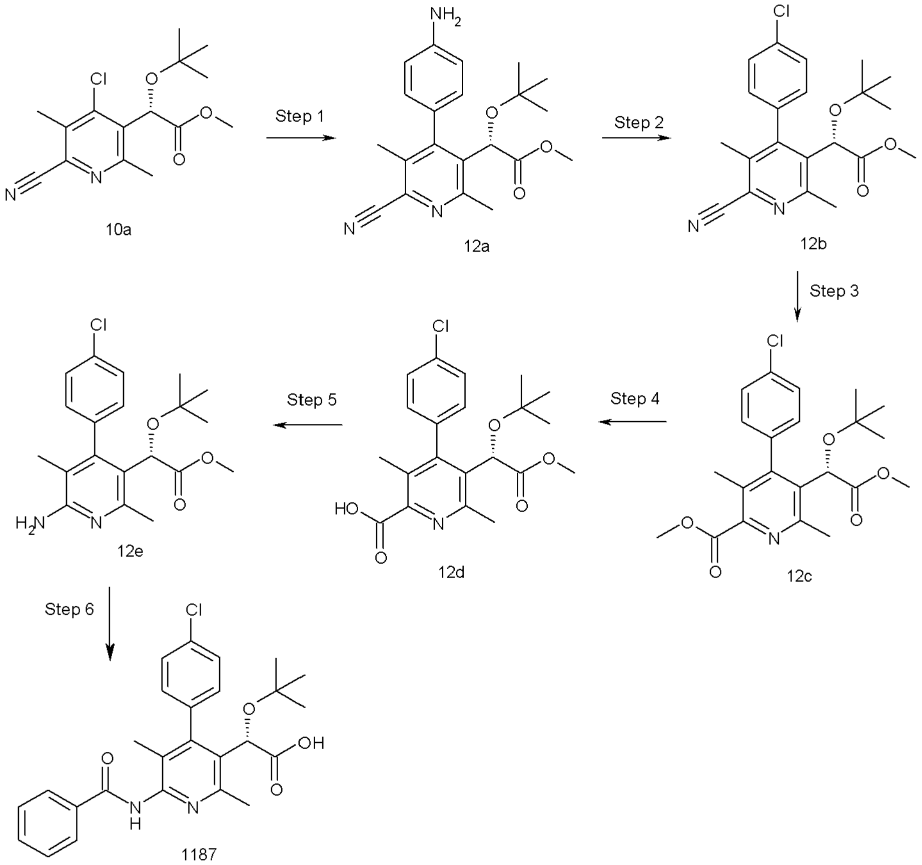


2h 10b

A mixture of $Pd(OAc)_2$ (70 mg, 0.31 mmol), 1,3- propylene bis(dicyclohexylphosphonium tetrafluoroborate (0.38 g, 0.63 mmol), dichloropyridine **2h** (Example 2) (2.0 g, 6.2 mmol) and potassium carbonate (1.3 g, 9.4 mmol) is added to dried 4Å molecular sieves (3.0 g) in an oven-dried round bottom flask (100 mL) equipped with Teflon® coated magnetic stir bar, sealed with a rubber septum and cooled under vacuum. The rubber septum is secured by wrapping with electrical tape and DMF (20 mL) and MeOH (2.5 mL, 62 mmol) are added via syringe. A balloon of CO is connected to the reaction vessel using a short length of rubber tubing (~ 1 in.), a needle adapter and a 20 G needle. The inert atmosphere is then exchanged for carbon monoxide by briefly exposing the reaction vessel to vacuum (1-2 sec) and backfilling with carbon monoxide (3 times). The reaction mixture is heated at 120°C and stirred vigorously for 16 h, then is allowed to cool to room temperature, and is diluted with EtOAc (20 mL), combined and filtered through a plug of Celite (eluting with EtOAc). The filtrate is washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by CombiFlash® Companion (EtOAc/hexanes) to give the diester **10b**.

EXAMPLE 12

SYNTHESIS OF COMPOUND 1187 (TABLE 1)



Step 1:

A mixture of nitrile **10a** (Example 10) (1.7 g, 5.4 mmol), 2-aminophenylboronic acid (1.0 g, 7.3 mmol), *bis*[tri-*t*-butylphosphine]palladium(0) (276 mg, 0.54 mmol), $NaHCO_3$ (2.25 g, 26.7 mmol), DMA (50 mL) and water (5 mL) is degassed by bubbling Ar(g) under sonication for 5 min. The mixture is heated to 130°C and stirred for 15 h, then cooled to RT and partitioned between EtOAc (225 mL) and water (200 mL). The aqueous layer is extracted with EtOAc (2 x 100 mL) and the combined organic layers are washed with water, dried over Na_2SO_4 and concentrated. The residue is purified by CombiFlash® Companion to give the aniline **12a**.

Step 2:

Aniline **12a** is converted to intermediate **12b** using the procedure described in step 2 of Example 5.

Step 3:

A mixture of **12b** (3.8 g, 9.8 mmol), aqueous NaOH (10N, 9.8 mL, 98 mmol) and EtOH (10 mL) is heated at 90 ºC in a sealed tube for 16 h. The mixture is cooled to RT and diluted with concentrated HCl (12N, 10 mL, 120 mmol) and water (500 mL). The mixture is extracted with EtOAc (3 x 500 mL) and the combined organic layers are dried over Na_2SO_4 and concentrated to dryness. The residue is taken up in MeOH (5 mL) and Et_2O (50 mL) and treated slowly with a hexane solution of $TMSCH_2N_2$ (2M, 3.5 mL, 15.0 mmol), and the mixture is stirred for 10 min, then evaporated to dryness. The residue is purified by CombiFlash® Companion to give the diester **12c**.

Step 4:

A mixture of diester **12c** (2.9 g, 6.9 mmol), THF (9 mL) and MeOH (3 mL) is treated with LiOH (1N, 9.7 mL, 9.7 mmol). The mixture is stirred for 10 min, then is acidified with aqueous HCl (1N, 15 mL, 15 mmol), diluted with brine and extracted with EtOAc (3 x 50 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give carboxylic acid **12d**.

Step 5:

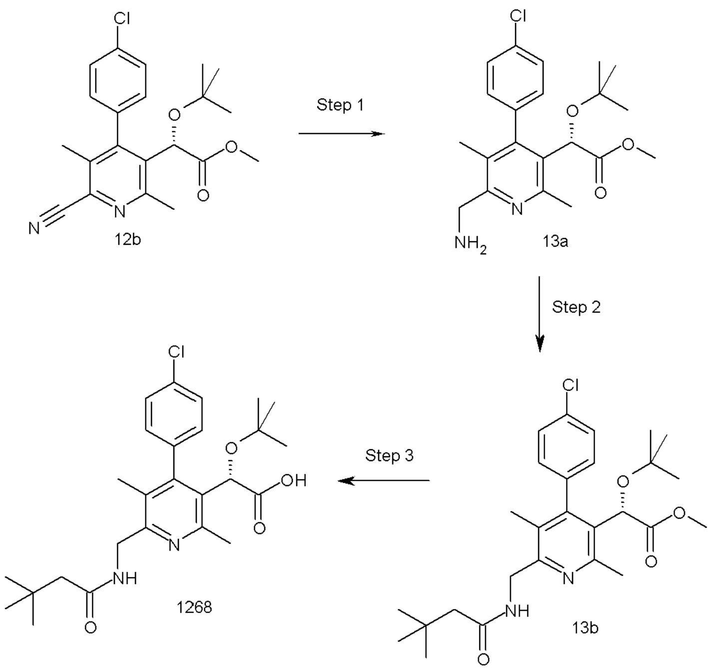
To a mixture of **12d** (1.9 g, 4.6 mmol) and Et_3N (1.3 mL, 9.3 mmol) in PhMe (63 mL) is added water (0.4 mL, 23 mmol) followed by DPPA (2.0 mL, 9.3 mmol). The mixture is heated at 90°C for 30 min, and then a further portion of DPPA (500 µL, 2.3 mmol) is added. Stirring is continued for 40 min and the mixture is cooled to RT, diluted with EtOAc (100 mL), and washed with saturated aqueous $NaHCO_3$, water and brine. The organic layer is dried over Na_2SO_4 and concentrated and the residue is purified by CombiFlash® Companion to give intermediate **12e**.

Step 6:

A mixture of aminopyridine **12e** (30 mg, 0.08 mmol) in THF (2 mL) is treated with Et_3N (22 µL, 0.16 mmol) followed by benzoyl chloride (12 µL, 0.10 mmol) and the mixture is heated at 50ºC for 2 h. The mixture is diluted with MeOH (0.5 mL), aqueous NaOH (5N, 80 µL, 0.40 mmol) is added, and the mixture is stirred at 55ºC for 2 h. The mixture is concentrated nearly to dryness and diluted with AcOH (1.5 mL) and DMF (0.5 mL), and purified by preparative HPLC to give compound **1187** (Table 1).

EXAMPLE 13

SYNTHESIS OF COMPOUND 1268 (TABLE 1)



Step 1:

A mixture of nitrile **12b** (Example 12) (6 g, 15.4 mmol) and AcOH (100 mL) is treated with 10% Pd/C (1.64 g, 1.54 mmol). The mixture is purged with hydrogen gas and stirred at RT for 1.5 h. The flask is evacuated several times and the catalyst is removed by filtration through Celite® with EtOAc washes. The mixture is concentrated *in vacuo* and the residue is taken up in EtOAc, washed with saturated $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and concentrated. The residue is purified by CombiFlash® Companion (1-10% MeOH/DCM gradient with 1% Et_3N) to afford after concentration, amine **13a**.

Step 2:

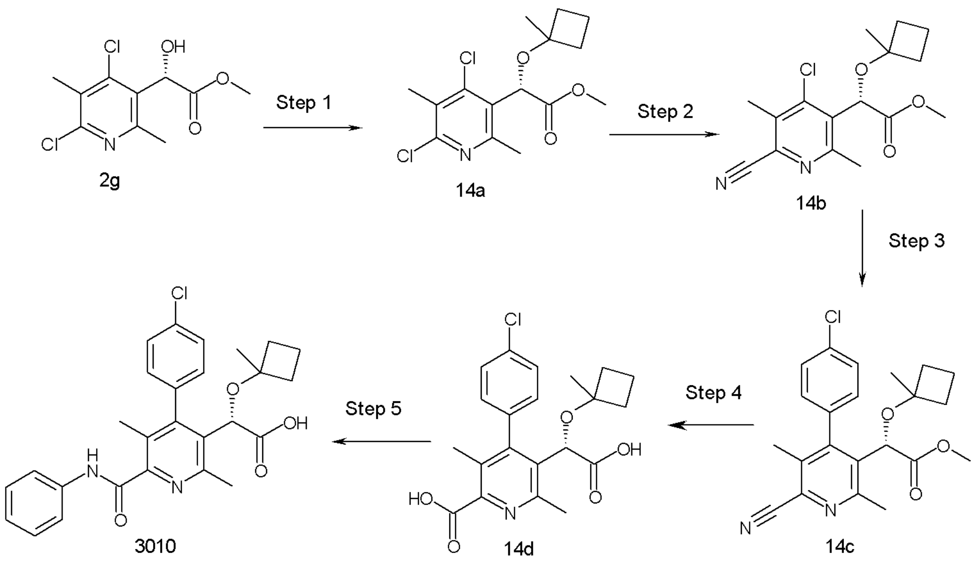
To a solution of amine **13a** (85 mg, 0.22 mmol) in DCM (2 mL) is added Et_3N (61 μL, 0.44 mmol) followed by t-butylacetyl chloride (34 μL, 0.24 mmol). The mixture is stirred at RT for 2 h and concentrated to dryness. The crude material containing amide **13b** is used in the following step.

Step 3:

A mixture of **13b** (106 mg, 0.22 mmol), MeOH (0.5 mL) and THF (1.5 mL) is treated with 5N NaOH (217 μL, 1.08 mmol). The mixture is stirred at 50°C for 16 h and concentrated to dryness. The residue is dissolved in AcOH/DMSO (1 mL each) and purified by preparative HPLC to afford after freezing and lyophilization, compound **1268** (Table 1).

EXAMPLE 14

SYNTHESIS OF COMPOUND 3010 (TABLE 3)



Step 1:

To solid P_2O_5 (652 mg, 4.6 mmol) in a dry RB flask is slowly added 85% H_3PO_4 (503 µL, 7.34 mmol) via syringe. This mixture is allowed to stir a few minutes; DCM (20 mL) is then added followed by alcohol **2g** (Example 2) (970 mg, 3.67 mmol). To this mixture is added $BF_3 \cdot Et_2O$ (931 µL, 7.34 mmol) and methylenecyclobutane (3.4 mL, 37 mmol). The mixture is stirred at RT for 2 h then is quenched rapidly with aqueous $NaHCO_3$. The reaction mixture is diluted with EtOAc, washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue is purified using the Combi-Flash® Companion (hexanes/EtOAc) to give ether **14a** and recovered starting alcohol **1g**.

Step 2:

A mixture of **14a** (825 mg, 2.48 mmol), $Zn(CN)_2$ (583 mg, 5 mmol), $Pd(PPh_3)_4$ (430 mg, 0.37 mmol) and DMA (12 mL) is sealed in a microwave vessel and heated in the microwave at 125°C (10 min) using a Biotage Initiator Sixty. The reaction mixture is cooled, poured into EtOAc and washed with saturated brine. The organic phase is dried over $MgSO_4$, filtered and concentrated and the residue is purified by

Combi-Flash® Companion (hexanes/EtOAc) to give nitrile **14b**.

Step 3:

Intermediate **14b** is transformed to intermediate **14c** using the procedure described in steps 1 and 2 of Example 12.

Step 4:

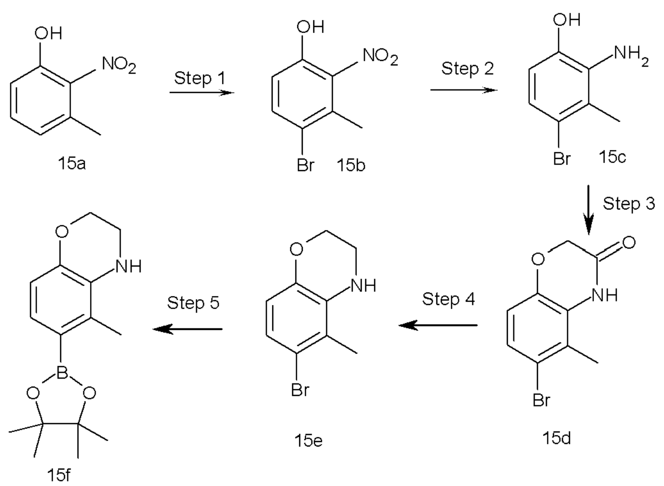
To nitrile **14c** (176 mg, 0.44 mmol) in MeOH (4 mL) is added 5 N NaOH (441 μL, 4.4 mmol). The mixture is heated at 65°C (24 h), cooled to RT, acidified with 1N HCl (pH ~1-2) and extracted with EtOAc (3x). The combined organic phases are dried ($MgSO_4$), filtered and concentrated to give diacid **14d**.

Step 5:

To a solution of diacid **14d** (181 mg, 0.45 mmol) in anhydrous THF (8 mL) is added Et_3N (263 μL, 1.9 mmol) and pivaloyl chloride (116 μL, 0.94 mmol) at RT and the mixture is stirred for 1 h. To a portion of this stock solution (2 mL, 0.11 mmol) is added aniline (11.3 μL, 0.12 mmol) and the mixture is allowed to stir at RT for 16 h. The reaction mixture is treated with 10 N NaOH (112 μL, 1.12 mmol) for 4 h and concentrated to dryness, purified by preparative HPLC and lyophilized to give compound **3010** (Table 3).

EXAMPLE 15

SYNTHESIS OF INTERMEDIATE 15F



Step 1:

A mixture of nitrophenol **15a** (5.23 g, 34.1 mmol) and AcOH (20 mL) is cooled in an ice bath and bromine (1.75 mL, 34.15 mmol, dissolved in 5 mL AcOH) is added dropwise with stirring. The mixture is stirred for about 1 h at 0°C and poured into ice water (250 mL). The mixture is extracted with EtOAc (2 X 100 mL), washed with 5% $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated to give **15b**. This material is used in the next step without further purification.

Step 2:

To a well stirred ethanol solution (75 mL) of **15b** (8.1 g, 34.9 mmol) is added $SnCl_2$ (20 g, 105 mmol) and the reaction mixture is stirred at reflux for 2.5 h. A further portion of $SnCl_2$ (2g, 10 mmol) is added and heating at reflux is continued for 1 h. The mixture is cooled to RT and poured onto ice (250 g), and the pH is adjusted to approximately 7.5 with aqueous 5% $NaHCO_3$. The mixture is extracted with EtOAc (3 X 100 mL) and the organic extract is washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to give the aniline intermediate **15c**.

Step 3:

To a stirred, ice cold, mixture of K_2CO_3 (2.05 g, 14.8 mmol), aniline **15c** (750 mg, 3.71 mmol) and DMF (5 mL) under nitrogen, is added chloroacetyl chloride (355 µL, 4.45 mmol) dropwise. The mixture is allowed to warm to RT over a period of about 15 min and is then heated to 60°C for 1 h. The mixture is allowed to cool to RT, is poured into a mixture of ice/water (250 mL) and is stirred for approximately 15 min. The suspension is centrifuged, and the supernatant is discarded. The solid material is left drying under suction overnight to give intermediate **15d**.

Step 4:

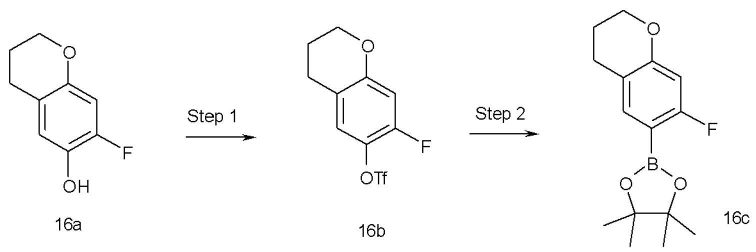
To an ice cold mixture of the cyclic amide **15d** (280 mg, 1.16 mmol) and THF (6 mL) under nitrogen is slowly added a borane-THF solution (1M in THF, 1.74 mL, 1.74 mmol). The reaction mixture is slowly allowed to warm to RT, then is stirred at RT for 1.5 h and then gently heated to reflux for 1 h. The mixture is cooled in an ice bath and is carefully quenched with aqueous 1 M NaOH (4 mL) over about 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) and saturated aqueous NaCl, and dried over anhydrous $MgSO_4$, filtered and concentrated to give **15e**.

Step 5:

A well stirred mixture of the arylbromide **15e** (0.50 g, 2.2 mmol), potassium acetate (728 mg, 7.7 mmol) and bis(pinacolato)diborane (0.83 g, 3.3 mmol) in DMF (15 mL) is degassed by bubbling Ar through the solution for about 20 min. $PdCl_2$(dppf)-DCM (320 mg, 0.44 mmol) is added and degassing is continued for about 15 min. The system is sealed (teflon screw cap vessel) under Ar and heated to 90°C for 5 h. The reaction mixture is allowed to cool to RT, diluted with EtOAc (150 mL), washed with brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The residue is purified by CombiFlash® Companion (EtOAc/hexanes) to give the desired boronate **15f**.

EXAMPLE 16

SYNTHESIS OF INTERMEDIATE 16C



Step 1:

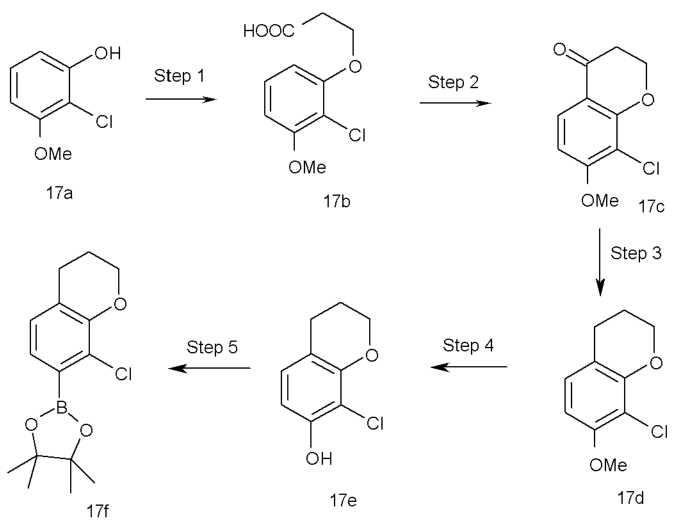
Neat Tf_2O (0.56 mL, 3.3 mmol) is added dropwise to a cooled (0°C) mixture of phenol **16a** (350 mg, 2.1 mmol; prepared according to Doi *et al Bull. Chem. Soc. Jpn.* **2004** *77*, 2257-2263) and pyridine (0.91 mL, 11 mmol) in DCM (10 mL) under an Ar atmosphere. The mixture is allowed to warm to RT and is stirred for 2 h. The reaction is quenched by the addition of a 10% citric acid solution (20 mL) and the mixture is extracted with DCM (3 x 20 mL). The combined organic layers are washed with water, dried over $MgSO_4$, filtered and concentrated to dryness. The residue is purified by CombiFlash® Companion to provide triflate **16b**.

Step 2:

A mixture of the triflate **16b** (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, and $PdCl_2$dppf-DCM complex (140 mg, 0.17 mmol) is added. The reaction mixture is degassed for an additional 5 min and heated to 100°C by microwave irradiation for 10 min, then cooled to RT. The mixture is diluted with EtOAc (60 mL) and washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue is further purified by CombiFlash® Companion to afford boronic ester **16c**.

EXAMPLE 17

SYNTHESIS OF INTERMEDIATE 17F



Step 1:

A solution of phenol **17a** (0.91 g, 5.74 mmol) in dry DMF (1 mL) is added dropwise to a mixture of NaH (60% in oil, 0.60 g, 15 mmol) in dry DMF (1 mL) cooled to 15°C and the mixture is stirred for 20 min. A solution of 3-bromopropionic acid (1.1 g, 6.9 mmol) in dry DMF (0.5 mL) is added dropwise and the mixture is stirred at RT overnight. After 16 h, MeOH (1.2 mL) is added and the reaction mixture is added to dilute HCl (12 mL of 1 N HCl in 100 mL water) and extracted with EtOAc (80 mL; the pH of the aqueous phase is adjusted to pH <3). The organic layer is dried over anhydrous Na_2SO_4, filtered and concentrated to give **17b** contaminated with some unreacted starting material.

Step 2:

A mixture of **17b** (1.53 g, 6.63 mmol) and polyphosphoric acid (7 g) is heated to 75°C. After 4 h, the reaction is cooled, and ice and water are slowly added with rapid stirring. The mixture is extracted with EtOAc (100 mL) and the organic extract is washed with water, saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated to give **17c** (crude).

Step 3:

AcOH (80 mL) is added to a mixture of chromanone **17c** (6.2 g, 29 mmol) and freshly activated zinc powder (38 g, 580 mmol). The mixture is stirred at 100°C for15 h and filtered through Celite, and the Celite pad is rinsed repeatedly with EtOAc (4 x 25 mL). The filtrate is concentrated and extracted with EtOAc (400 mL) and the organic extract is washed with saturated $NaHCO_3$ (2 x 400 mL) and brine (200 mL). The organic phase is dried over $MgSO_4$ and evaporated to provide crude chromane **17d**.

Step 4:

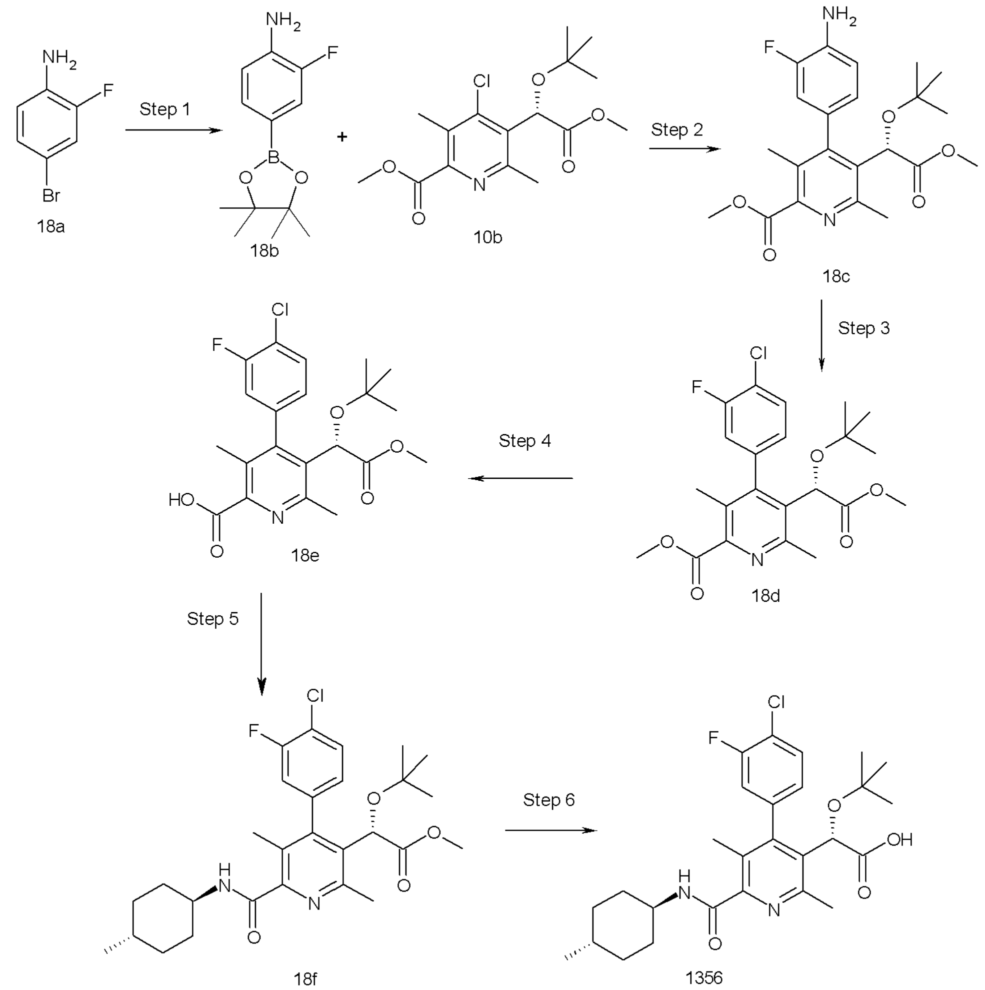
A mixture of anisole **17d** (4.0 g, 20 mmol) and dry dichloromethane (40 mL) is cooled to -78°C. A BBr_3 solution (1M in DCM, 44 mL, 44 mmol) is added dropwise and then the reaction mixture is removed from the dry ice bath. After 45 min, the mixture is cooled (ca. 0°C) and the reaction is quenched with water (25 mL) added dropwise. The mixture is diluted with water (400 mL) and is carefully neutralized with saturated aqueous $NaHCO_3$ (final pH ca 8). This mixture is then extracted with DCM (300 mL and then 100 mL) and the combined organic layers are dried over Na_2SO_4 and evaporated to dryness. The product is purified by CombiFlash® Companion to provide phenol **17e**.

Step 5:

Compound **17e** is transformed to compound **17f** using the procedure described in steps 1 and 2 of Example 16.

EXAMPLE 18

SYNTHESIS OF COMPOUND 1356 (TABLE 1)



Step 1:

To a mixture of bromide **18a** (1.0 g, 5.3 mmol), *bis*-(pinacolato)diboron (1.9 g, 7.4 mmol) and potassium acetate (1.6 g, 16 mmol) is added anhydrous DMF (20 mL) and the mixture is deoxygenated by bubbling a stream of N_2 gas through the mixture for about 25 min. 1,1'-Bis(diphenylphosphino)ferrocene (0.58 mg, 0.79 mmol) is added and the mixture is deoxygenated for approximately a further 5 min, then heated to 95°C. After 5 h, the reaction mixture is cooled, diluted with EtOAc (200 mL) and washed with brine (2 x 100 mL). The layers are filtered through a pad of Celite and reseparated. The organic phase is dried over anhydrous $MgSO_4$, filtered and concentrated and the residue is purified by CombiFlash® Companion

(EtOAc/hexanes) to afford the boronate **18b**.

Step 2:

Intermediate **18b** is coupled to intermediate **10b** (Example 10) using the procedure described in step 1 of Example 12 to give intermediate **18c**.

Step 3:

Intermediate **18c** is transformed to intermediate **18d** using the procedure described in step 2 of Example 5.

Step 4:

Intermediate **18d** is transformed to intermediate **18e** using procedure described in step 4 of Example 12.

Step 5:

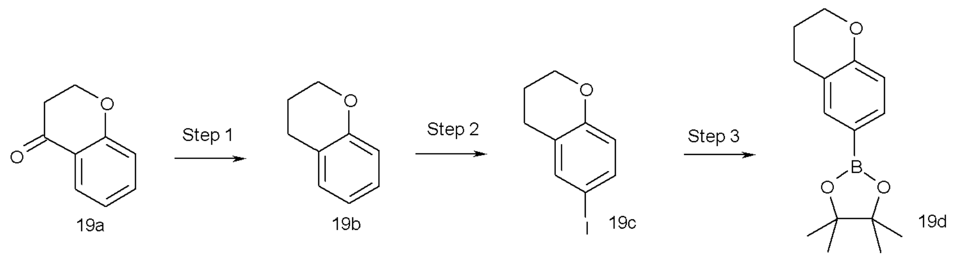
A mixture of carboxylic acid **18e** (44 mg, 0.10 mmol) in NMP is treated with Et_3N (58 µL, 0.42 mmol) and TBTU (67 mg, 0.21 mmol). The mixture is stirred for 5 min and *trans*-4-methylcyclohexylamine (35 µL, 0.31 mmol) is added. The mixture is stirred for 1 h, diluted with EtOAc (40 mL), washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude mixture is purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to afford the desired amide **18f**.

Step 6:

A mixture of amide **18f** (42 mg, 0.080 mmol), THF (1.5 mL) and MeOH (0.75 mL) is treated with 1.0 N LiOH (0.75 mL, 0.75 mmol). The mixture is stirred at 55°C for 1 h, neutralized with AcOH and purified by preparative HPLC. A mixture of the product and DCM (3 mL) is adjusted to pH > 10 with 1N NaOH and neutralized with AcOH. The mixture is passed through a phase separator filter and the organic layer is concentrated *in vacuo*, diluted with a mixture of MeCN / water and lyophilized to give compound **1356**.

EXAMPLE 19

SYNTHESIS OF INTERMEDIATE 19D



Step 1:

A mixture of chromanone **19a** (9.78 g, 66.0 mmol) and AcOH (20 mL) is added to a mixture of zinc dust (108 g, 1.65 mol) in AcOH (150 mL). The mixture is heated to 100°C and is stirred overnight, then filtered through Celite® (washed with EtOAc, 100mL), diluted with PhMe (300 mL) and concentrated to give intermediate **19b**.

Step 2:

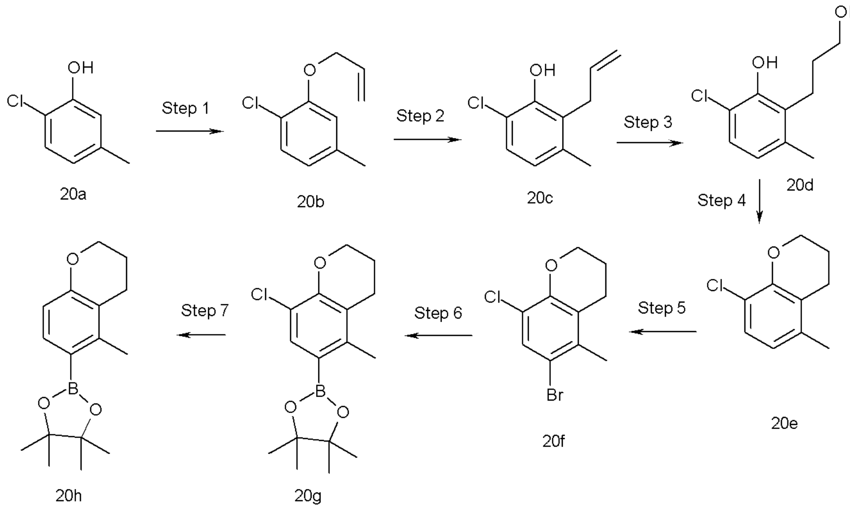
$AgNO_3$ (12.0 g, 70.6 mmol) and I_2 (15.8 g, 62.3 mmol) are added sequentially to a mixture of **19b** (8.45 g, 63.0 mmol) and MeOH (225 mL). The mixture is allowed to stir for about 1 h and filtered through Celite®, and the filtrate is concentrated under reduced pressure. The residue is diluted with EtOAc (250 mL) and washed with saturated sodium thiosulfate (250 mL). The organic layer is washed with water (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue is further purified by CombiFlash® Companion to give 6-iodochroman **19c**.

Step 3:

A mixture of the 6-iodochroman **19c** (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 about 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (314 mg, 0.38 mmol). The reaction mixture is then degassed for about an additional 5 min and heated to 95°C for 5 h. The mixture is then cooled to RT, diluted with water and extracted with EtOAc (3 x 100 mL). The combined organic extracts are washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue is further purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to afford intermediate **19d**.

EXAMPLE 20

SYNTHESIS OF INTERMEDIATE 20H



Step 1:

A mixture of phenol **20a** (6.75 g, 47.3 mmol) and DMF (270 mL) is treated with allyl bromide (6.55 mL, 75.7 mmol). To this mixture, NaH (60%, 4 g, 99.4 mmol) is added portionwise and stirring is continued overnight. The reaction mixture is diluted with EtOAc (500 mL) and washed with H_2O. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness to obtain the desired product **20b**.

Step 2:

The ether **20b** (8.6 g) is stirred and heated at 240°C for 20 min in a microwave vial to provide **20c**.

Step 3:

To a mixture of the allyl intermediate **20c** (9.3 g, 45.8 mmol) in anhydrous THF (300 mL) at 0°C is added borane (1 M in THF, 96 mL, 96 mmol, 2.1 eq). The mixture is allowed to warm to RT and then is stirred for 2.5 h. The mixture is then cooled to 0°C and treated with 10 N NaOH dropwise, followed by slow addition of 30% H_2O_2 (104 ml, 916 mmol). The resulting mixture is allowed to warm to RT and is stirred at RT for 1 h. The reaction mixture is diluted with HCl (10%, 100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phases are dried over $MgSO_4$ and concentrated. The residue is purified by CombiFlash® Companion to give **20d**.

Step 4:

To a mixture of the diol **20d** (7.1 g, 35.3 mmol) in THF (500 mL) are added PPh_3 (12 g, 45.9 mmol), followed by DEAD (7.2 mL, 45.9 mmol). The mixture is stirred at RT for 4 h. The reaction mixture is concentrated under reduced pressure and purified by CombiFlash® Companion to obtain the desired product **20e**.

Step 5:

A mixture of the chroman derivative **20e** (5.26 g, 28.8 mmol) and AcOH (70 mL) is treated with Br_2 (19.2 mL, 37.4 mmol) in AcOH (40 mL). The mixture is stirred at RT for 15 min, then diluted with toluene and concentrated to dryness. The residue is taken up in EtOAc (25 mL) and washed with saturated $Na_2S_2O_3$ (25 mL) and saturated $NaHCO_3$ (25 mL). The organic layer is dried over $MgSO_4$, concentrated and purified by CombiFlash® Companion to obtain the desired product **20f**.

Step 6:

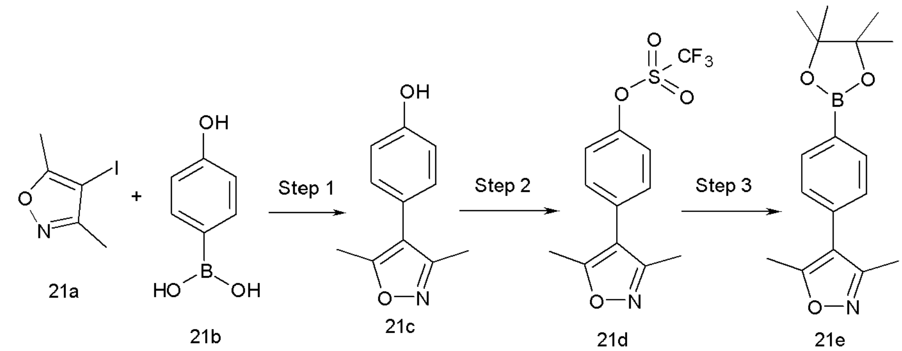
A mixture of bromide **20f** (2.71 g, 10.4 mmol) and DMF (120 mL) is treated with bispinacolatoborane (4 g, 15.5 mmol) and potassium acetate (3.45 g, 36.3 mmol). The mixture is degassed (using an Ar balloon) and $PdCl_2$dppf (845 mg, 1.04 mmol) is added. The mixture is degassed again (using an Ar balloon) and heated at 95°C for 16 h. The mixture is cooled to RT, diluted with H_2O (300 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers are washed with water, dried over $MgSO_4$, filtered and concentrated. The residue is purified by CombiFlash® Companion and is triturated with hexanes to provide intermediate **20g**.

Step 7:

Palladium on activated charcoal (10% Pd by weight, 0.63 mg, 0.59 mmol) is added to a solution of aryl chloride **20g** (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®, and the Celite® pad is rinsed with MeOH. The filtrate is concentrated to dryness and the residue partitioned between water and EtOAc (10 mL each). The organic layer is dried over anhydrous $MgSO_4$ and concentrated to obtain boronic ester **20h**.

EXAMPLE 21

SYNTHESIS OF INTERMEDIATE 21E



Step 1:

A mixture of **21a** (1.0 g, 4.5 mmol), **21b** (0.72 g, 5.2 mmol), potassium carbonate (1.6 g, 12 mmol) and *trans*-dichlorobis(triphenylphosphine)palladium (II) (0.36 g, 0.62 mmol) in DMF (8.3 mL) and water (0.88 mL) is heated under microwave for 15 min at 130°C. The mixture is partitioned between EtOAc (25 mL) and water (25 mL) and the organic layer is washed with water, dried over Na_2SO_4, filtered and concentrated. The residue is purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to afford the desired alcohol **21c**.

Step 2:

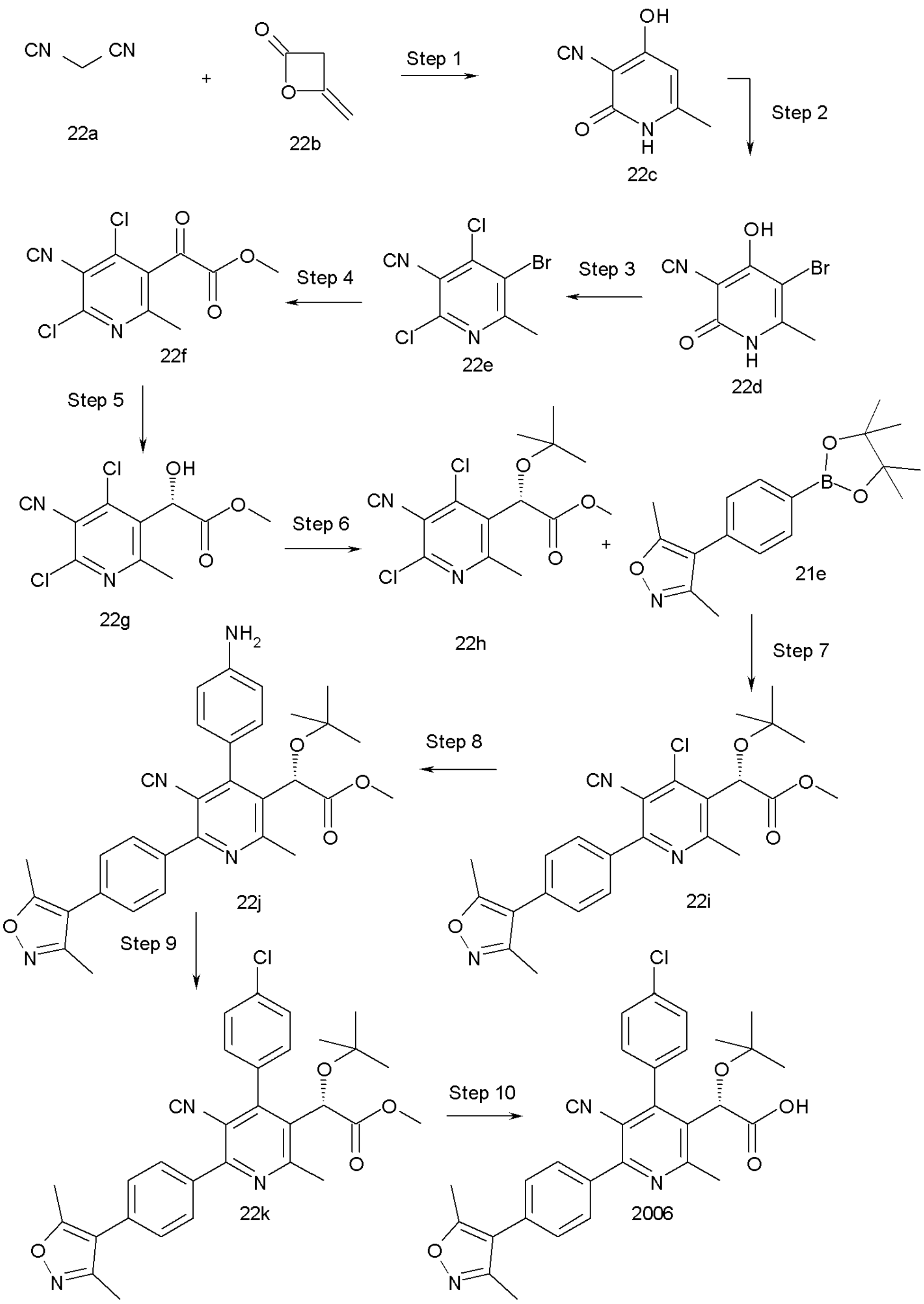
A mixture of alcohol **21c** (0.70 g, 3.7 mmol) in pyridine (15 mL) is treated with Tf_2O (0.95 mL, 5.6 mmol) and stirred at 23°C for 30 min. The mixture is concentrated and the residue is partitioned between DCM (50 mL) and 10% HCl (50 mL). The organic layer is washed with 10% HCl and saturated $NaHCO_3$ solution and passed through a phase separator. Evaporation of the organic layer gives the triflate **21d**.

Step 3:

A solution of the triflate **21d** (1.2 g, 3.7 mmol), bis(pinacolato)diborane (1.4 g, 5.5 mmol) and potassium acetate (1.2 g, 13 mmol) in DMF (50 mL) is degassed with Ar for about 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (0.39 mg, 0.48 mmol). The reaction mixture is then degassed for about an additional 5 min before being heated to 95°C overnight. The reaction mixture is then cooled to RT, diluted with water (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts are washed with water, dried over Na_2SO_4, filtered and concentrated. The residue is purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to give borane **21e**.

EXAMPLE 22

SYNTHESIS OF COMPOUND 2006 (TABLE 2)



Step 1:

4-Hydroxypyridone **22c** is synthesized using the procedure described by T. Kato; Y. Kubota; M. Tanaka; H. Takahashi and T. Chiba; *Heterocycles* **1978**, *9*, 811.

Step 2:

Intermediate **22c** is transformed to intermediate **22d** using procedures described in step 2 of Example 2.

Step 3:

Intermediate **22d** is transformed to intermediate **22e** using procedures described in step 3 of Example 2.

Step 4:

Intermediate **22e** is transformed to intermediate **22f** using procedures described in step 4 of Example 2.

Step 5:

Intermediate **22f** is transformed to intermediate **22g** using procedures described in step 5 of Example 2.

Step 6:

Intermediate **22g** is transformed to intermediate **22h** using procedures described in step 6 of Example 2.

Step 7:

Intermediate **22h** is transformed to intermediate **22i** using procedures described in step 1 of Example 4.

Step 8:

Intermediate **22i** is transformed to intermediate **22j** using procedures described in step 1 of Example 5.

Step 9:

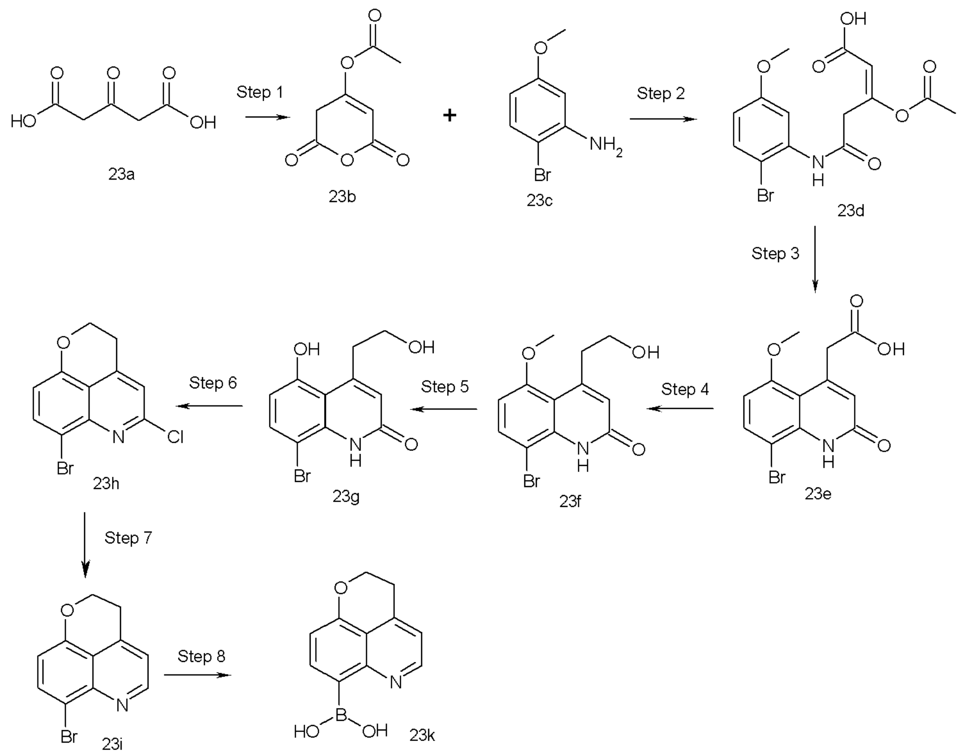
Intermediate **22j** is transformed to intermediate **22k** using procedures described in step 2 of Example 5.

Step 10:

Intermediate **22j** is transformed to compound **2006** using procedures described in step 3 of Example 4.

EXAMPLE 23

SYNTHESIS OF INTERMEDIATE 23K



Step 1:

1,3-acetonedicarboxylic acid **23a** (30 g; 205.3 mmol) is added in portions to Ac_2O (55 g; 587.7 mmol) and the mixture is stirred at 35°C for 23 h, then filtered. The filtrate is diluted with benzene (200 mL) and the solution stored at 5°C for 3 h. The precipitate is filtered and dried under vacuum to give intermediate **23b**.

Step 2:

To a stirred solution of aniline **23c** (7.5 g, 44 mmol) in AcOH (50 mL) is added **23b** (8.0 g, 40 mmol) portionwise. The reaction mixture is warmed to 35°C for 2 h, then 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 **23d**.

Step 3:

Intermediate **23d** (5.7 g, 15.4 mmol) is added portionwise to concentrated sulfuric acid (20 mL) at RT, so that the temperature of the reaction mixture is kept below 30°C during addition. The mixture is stirred at RT for 30 min and poured in ice/water (400 mL). The resulting precipitate is isolated by filtration, rinsed with water and dried under vacuum to give **23e**.

Step 4:

A solution of borane (1.0 M in THF, 10.5 ml, 10.5 mmol) is added dropwise to an ice cold solution of quinolone **23e** (1.5 g, 4.8 mmol) in dry THF (40 mL) under a N_2 atmosphere. The mixture is allowed to warm to RT and stirred for 22 h. An additional equivalent of BH_3 is added at 0°C and the reaction mixture is heated to 45°C for 2 h. The reaction is carefully quenched witn 1.0 N NaOH (10 mL) and THF is removed under vacuum. The mixture is poured in EtOAc (100 mL) and the precipitate is collected by filtration and dried under vacuum to provide **23f**.

Step 5:

To a mixture of **23f** (1.1 g, 3.8 mmol) and DCM (60 mL) at -78°C is added dropwise a 1.0 M BBr_3 solution (23 mL, 23 mmol). The cooling bath is removed after 1 h and the mixture is stirred at RT for 16 h. The mixture is poured in ice/water (100 mL) and the precipitate is collected by filtration and dried under vacuum to give **23g**.

Step 6:

To a solution of intermediate **23g** (773 mg, 2.27 mmol) in THF (30 mL) is added PPh_3 (928 mg, 3.5 mmol) followed by DIAD (0.69 ml, 3.5 mmol) (dropwise), and the solution is stirred at RT for 2 h. The reaction mixture is concentrated under vacuum and the crude product is directly added portionwise to $POCl_3$ (2 mL) at RT. The reaction mixture is stirred at 100°C for 45 min and then cooled to room temperature. The mixture is concentrated under vacuum and the crude product is diluted with DCM. The organic phase is washed with 1.0 N NaOH, water, and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product is purified by combiFlash® (Hex/EtOAc 9/1 to 1/1) to give **23h**.

Step 7:

To a solution of chloroquinoline **23h** (300 mg, 1 mmol) in TFA (10 mL) is added zinc (340 mg, 5 mmol) and the mixture is stirred at RT for 16 h. The mixture is filtered and concentrated under vacuum, and the residue is diluted with 1.0 N NaOH (50 mL) and extracted with DCM (3x). The combined organic extracts are washed with water and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue is purified by combiFlash® (Hex/EtOAc 6/4 to 4/6) to give **23i**.

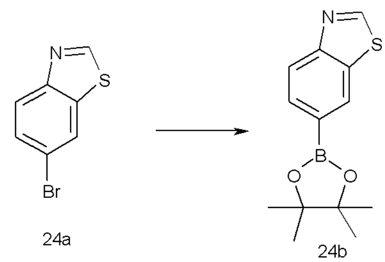
Step 8:

A mixture of aryl halide **23i** (5 g, 20 mmol) Et_2O (400 mL) under a nitrogen atmosphere is heated to 43°C then cooled to -75°C in a dry ice/acetone bath. n-

Butyllithium solution (1.38 M in hexanes, 21.7 mL, 30 mmol) is added dropwise (4 min addition time, internal temp below 70°C). The mixture is stirred for an additional 5 min and n-butyllithium solution (880 μL, 1.2 mmol) is added. After 5 min, triisopropyl borate (16.9 mL, 72 mmoles) is added while the temperature is held at -74ºC. The reaction mixture is allowed to warm to -42°C and 5 mL (21 mmol) of triisopropylborate are added. The mixture is stirred for 10 min at -18°C,and 2.5 mL (11 mmol) of triisopropylborate followed by aqueous 2 N HCl (200 mL, 400 mmol) are added. The mixture is allowed to stir at room temperature for 2.5 h, then is diluted with Et_2O (50 mL) and 2N HCl (50 mL). (The layers are separated and the aqueous layer is adjusted to pH = 7 with 10N NaOH (45 mL) and 1N NaOH (20 mL). The precipitate is filtered and dried for 16 h at high vacuum affording the desired compound **23k**.

EXAMPLE 24

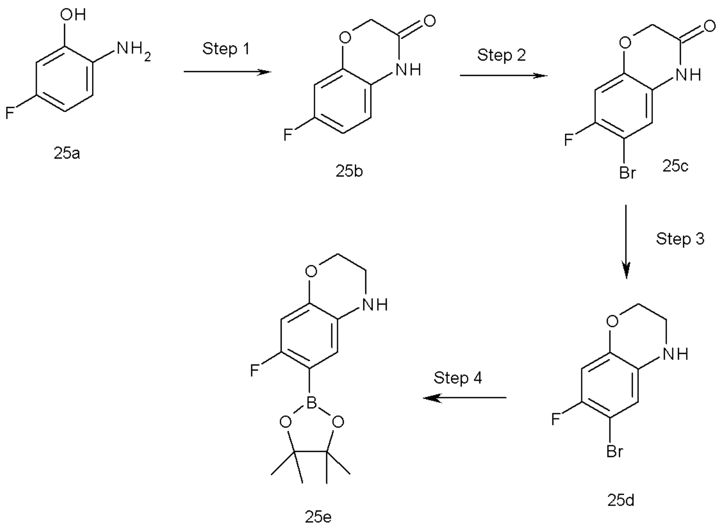
SYNTHESIS OF INTERMEDIATE 24B



To a mixture of the bromide **24a** (152 mg, 0.71 mmol) and DMF (5 mL) is added bis(pinacolato)diboron (234 mg, 0.92 mmol) and KOAc (210 mg, 2.13 mmol). The solution is degassed with argon gas under sonication (10 min) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (87 mg, 0.10 mmol) is added. The mixture is heated at 90°C for 16 h and cooled to RT. The mixture is diluted with EtOAc, washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue is purified using the CombiFlash® Companion (hexanes/EtOAc) to give the boronate **24b**.

EXAMPLE 25

SYNTHESIS OF INTERMEDIATE 25E



Step 1:

To a cold (0°C) mixture of **25a** (15.0 g, 118 mmol) and DMF (180 mL) is added K_2CO_3 (48.9 g, 354 mmol) followed by dropwise addition of chloroacetyl chloride (9.40 mL, 118 mmol). The reaction mixture is allowed to warm to RT and then heated to 60°C for 2 h. The reaction mixture is cooled to RT, poured into ice-water (2.0 L) and stirred for 30 min. The mixture is filtered and the solid rinsed with water and dried under reduced pressure to provide **25b**.

Step 2:

To a cooled (10°C) mixture of **25b** (12.4 g, 74.4 mmol), DCM (150 mL) and glacial Ac_2O (150 mL) is added dropwise over 1.5 hours, a solution of Br_2 (4.6 mL, 89 mmol) in DCM (75 mL). After 2 hours at 10°C, an additional amount of Br_2 (2.30 mL, 44.6 mmol) in DCM (40 mL) is added over 1 h with stirring at 10°C. Stirring is continued for 1 h and the reaction mixture is concentrated under reduced pressure. The residue is triturated with Et_2O (500 mL) to provide bromide **25c**.

Step 3:

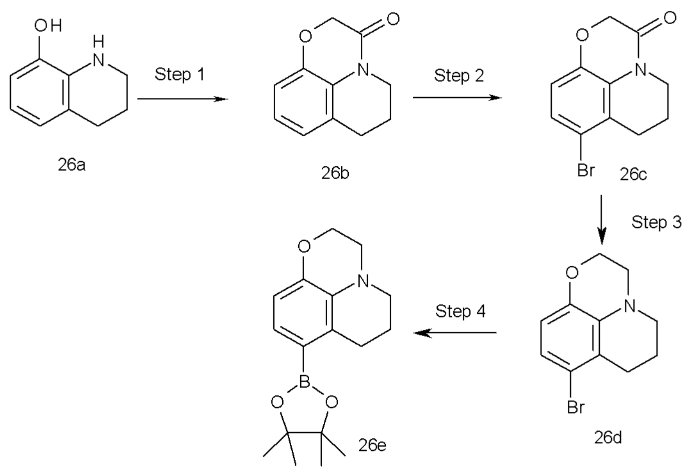
To a solution of **25c** (13.4 g, 54.5 mmol) in THF (300 mL) is added slowly borane-methyl sulfide complex (55.0 mL, 2.0 M solution in THF, 110 mmol) at 0°C. The mixture is allowed to warm to room temperature and then stirred at reflux for 1 h. The reaction mixture is cooled to 0°C, quenched slowly with 1 M aqueous HCl (27 mL), and then refluxed for 1 h. The mixture is diluted with Et_2O, neutralized with 1 M aqueous NaOH and after further extraction is concentrated. The residue is purified by flash column chromatography (15 to 30% EtOAc/hexanes) to provide intermediate **25d**.

Step 4:

A mixture of **25d** (10.0 g, 43.1 mmol), bis(pinacolato)diboron (16.4 g, 64.7 mmol) and KOAc (12.7 g, 129 mmol) in 1,4-dioxane (430 mL) is degassed with nitrogen for 30 min at RT and heated at 100°C under a nitrogen atmosphere. After 30 min, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (3.5 g, 4.3 mmol) is added and stirring is continued at 100°C (15 h). The reaction mixture is cooled to RT and filtered through a pad of Celite®. The Celite® pad is rinsed with EtOAc and the combined filtrate is concentrated under reduced pressure. The residue is purified by flash column chromatography (twice with 25% EtOAc/hexanes followed by 5 % EtOAc/DCM) to provide **25e**.

EXAMPLE 26

SYNTHESIS OF INTERMEDIATE 26E



Step 1:

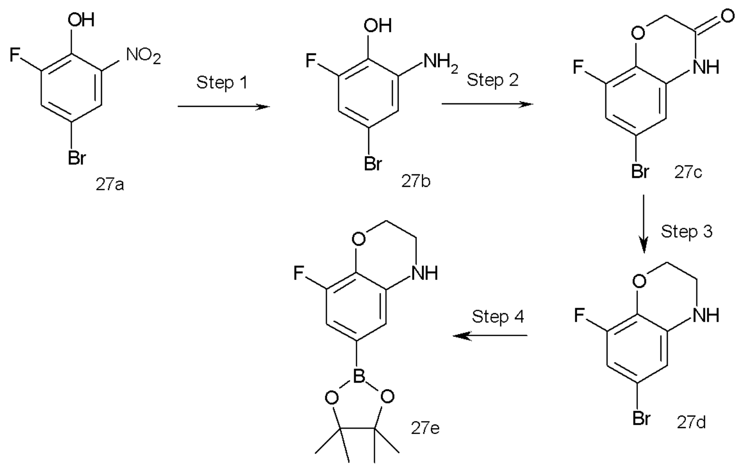
To a cold (0°C) solution of 1,2,3,4-tetrahydroquinolin-8-ol **26a** (6.00 g, 40 mmol) in DMF (60 mL) is added K_2CO_3 (16.7 g, 121 mmol) followed by dropwise addition of chloroacetyl chloride (4.25 mL, 53.6 mmol). The reaction mixture is warmed to RT and heated at 60°C for 2 h. The reaction mixture is cooled to RT, poured into ice-water (1.5 L) and stirred for 30 min. The resulting mixture is filtered and the solid rinsed with water and dried under reduced pressure (16 h) to provide amide **26b**.

Steps 2, 3, and 4:

Intermediate **26b** is transformed to intermediate **26e** using procedures described in steps 2 to 4 of Example 25.

EXAMPLE 27

SYNTHESIS OF INTERMEDIATE 27E



Step 1:

To a mixture of 4-bromo-2-fluoro-6-nitrophenol **27a** (12.0 g, 51 mmol) and EtOH (375 mL) is added a solution of sodium dithionite (35.4 g, 203 mmol) in water (125 mL). The mixture is heated at reflux for 1 h, then cooled to 0°C and slowly neutralized with saturated aqueous $NaHCO_3$ (150 mL). The mixture is concentrated and the residue is triturated with 10% MeOH/EtOAc (1.0 L) and filtered through a pad of Celite®. Concentration of the filtrate under reduced pressure provides aniline **27b**.

Step 2:

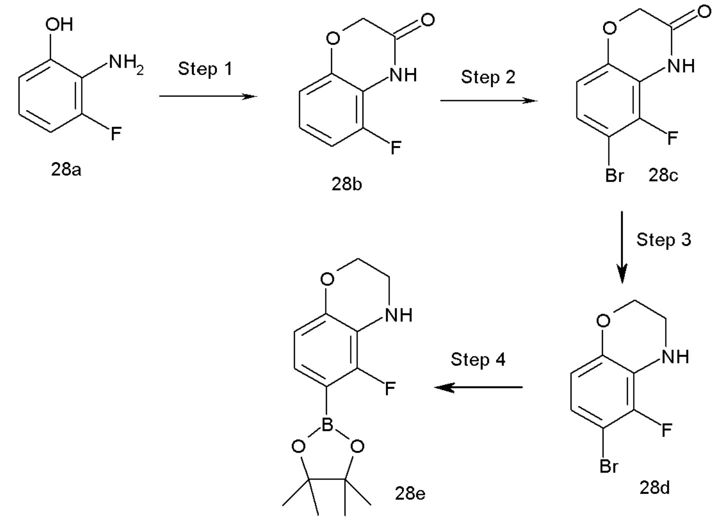
Intermediate **27b** is transformed to intermediate **27c** using the procedure described in step 1 of Example 25.

Steps 3 and 4:

Intermediate **27c** is transformed to intermediate **27e** using the procedures described in steps 3 and 4 of Example 25.

EXAMPLE 28

SYNTHESIS OF INTERMEDIATE 28E

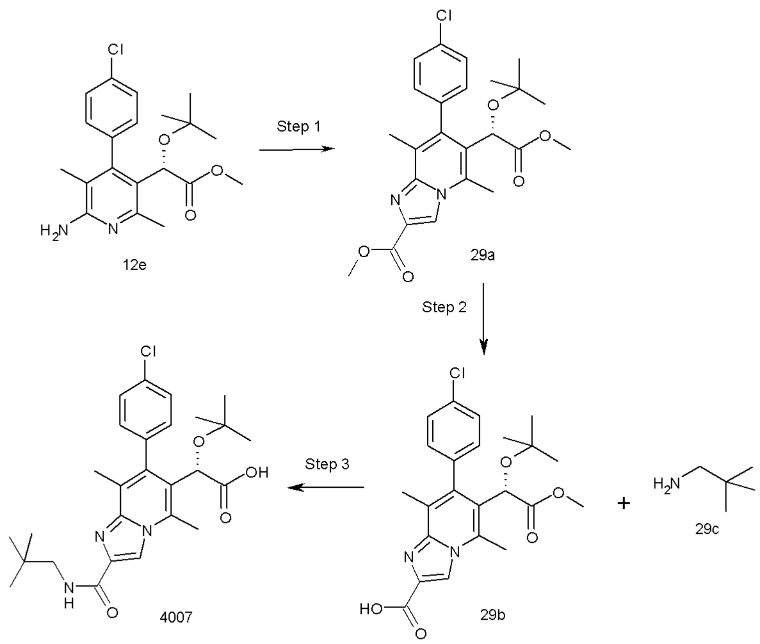


Steps 1 to 4:

Intermediate **28a** is transformed to intermediate **28e** using procedures described in steps 1 through 4 of Example 25.

EXAMPLE 29

SYNTHESIS OF COMPOUND 4007 (TABLE 4)



Step 1:

To a mixture of **12e** (Example 12) (570 mg, 1.5 mmol), EtOH (11 mL) and acetone (2.2 mL) is added $NaHCO_3$ (197 mg, 1.6 mmol) and methyl bromopyruvate (177 μL, 1.7 mmol). The mixture is heated at 85°C for 16 h and solvents are evaporated *in vacuo*. The residue is dissolved in DCM (20 mL), washed twice with water, dried over $MgSO_4$ and concentrated *in vacuo* giving **29a**.

Step 2:

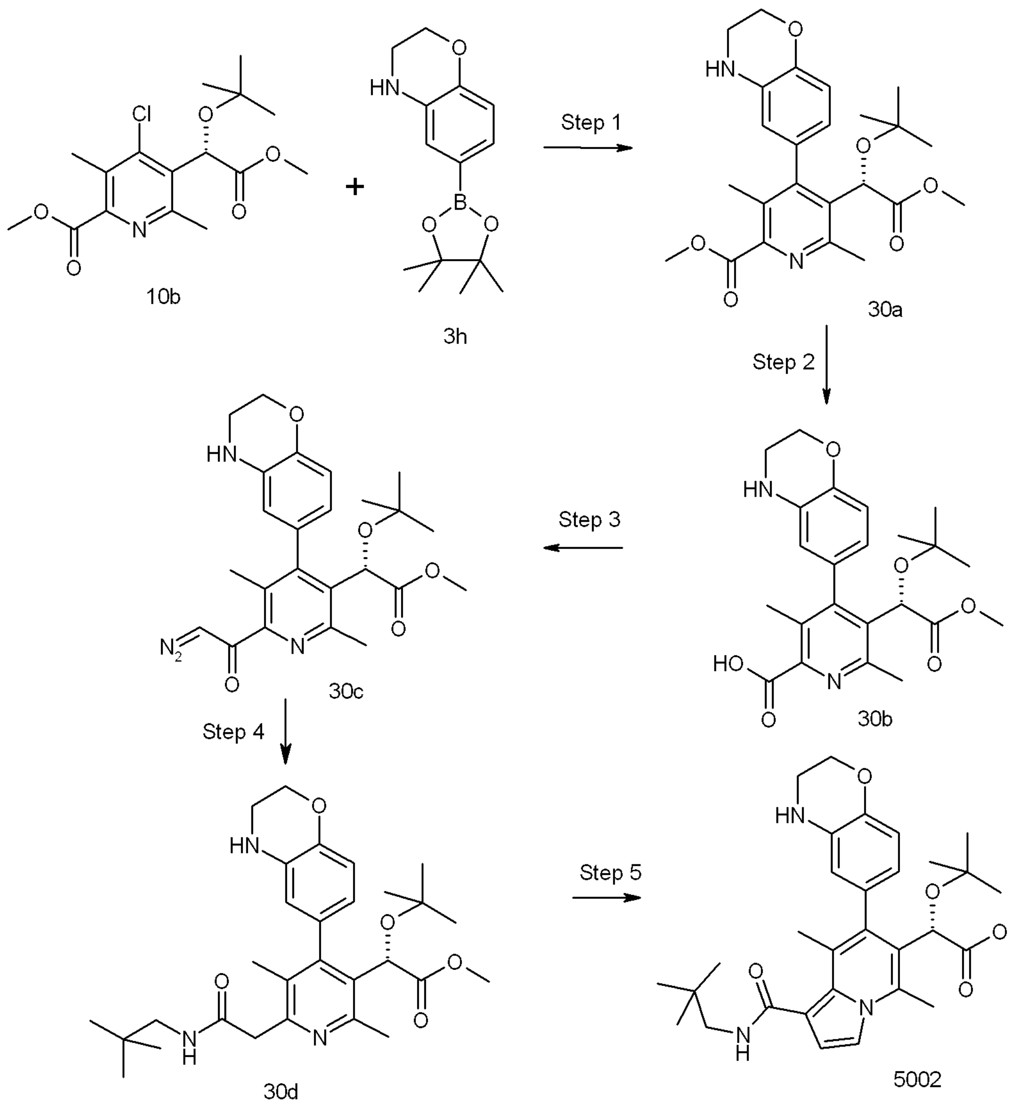
A mixture of **29a** (620 mg, 1.4 mmol), THF (18.7 mL) and MeOH (6.2 mL) is treated with LiOH (1N, 1.4 mL, 1.4 mmol) at 23ºC for 15 h. A further portion of 1N LiOH (1.4 mL, 1.4 mmol) is added and the mixture is stirred for 4 h at 23ºC. 1N NaOH (0.1 mL, 0.1 mmol) is then added and reaction is continued until complete conversion to product is detected by UPLC-MS. The mixture is adjusted to pH 1 with 1N HCl and extracted with DCM (3x), and the organic extract is dried over $MgSO_4$. The residue is purified by CombiFlash® (5% MeOH / 94 % DCM / 1% AcOH) affording pure **29b**.

Step 3:

To a mixture of **29b** (50 mg, 0.11 mmol) and NMP (1 mL) is added Et_3N (63 μL, 0.45 mmol), followed by N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (72 mg, 0.22 mmol). The mixture is stirred for 10 min, treated with neopentylamine **29c** (30 mg, 0.34 mmol) and stirred 16 h at 23ºC. 1N NaOH (0.5 mL, 0.5 mmol) is added to the reaction mixture and stirring is continued for 2 h at 60°C. The solution is neutralized with AcOH and EtOAc (75 mL) is added. The organic layer is washed with water and brine, dried over $MgSO_4$, filtered and concenrated *in vacuo* and the residue is purified by prep HPLC. A mixture of the product and DCM (3 mL) is treated with 1N NaOH (pH > 10) and neutralized with AcOH. The mixture is passed through a phase separator filter and the organic layer is concentrated *in vacuo*. The residue is diluted with a mixture of MeCN / water and lyophilized to give compound **4007**.

EXAMPLE 30

SYNTHESIS OF COMPOUND 5002 (TABLE 5)



Step 1:

Intermediates **10b** (Example 10) and **3h** (Example 3) are transformed to intermediate **30a** using the procedure described in step 2 of Example 4.

Step 2:

Intermediate **30a** is transformed to intermediate **30b** using the procedure described in step 4 of Example 12.

Step 3:

To a mixture of **30b** (700 mg, 1.5 mmol), Et_3N (420 μL, 3.0 mmoles) and THF (15 mL) at 0°C is added isobutyl chloroformate (205 μL, 1.6 mmol) dropwise. The mixture is stirred at 0°C for 30 min, and diazomethane (0.67 M in Et_2O, 11.2 mL, 7.5 mmol) is added. The mixture is allowed to reach 23°C and stirred for 2 h, then is concentrated *in vacuo*. A mixture of EtOAc and water is added to the residue, the layers are separated and the organic layer is washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* affording **30c**.

Step 4:

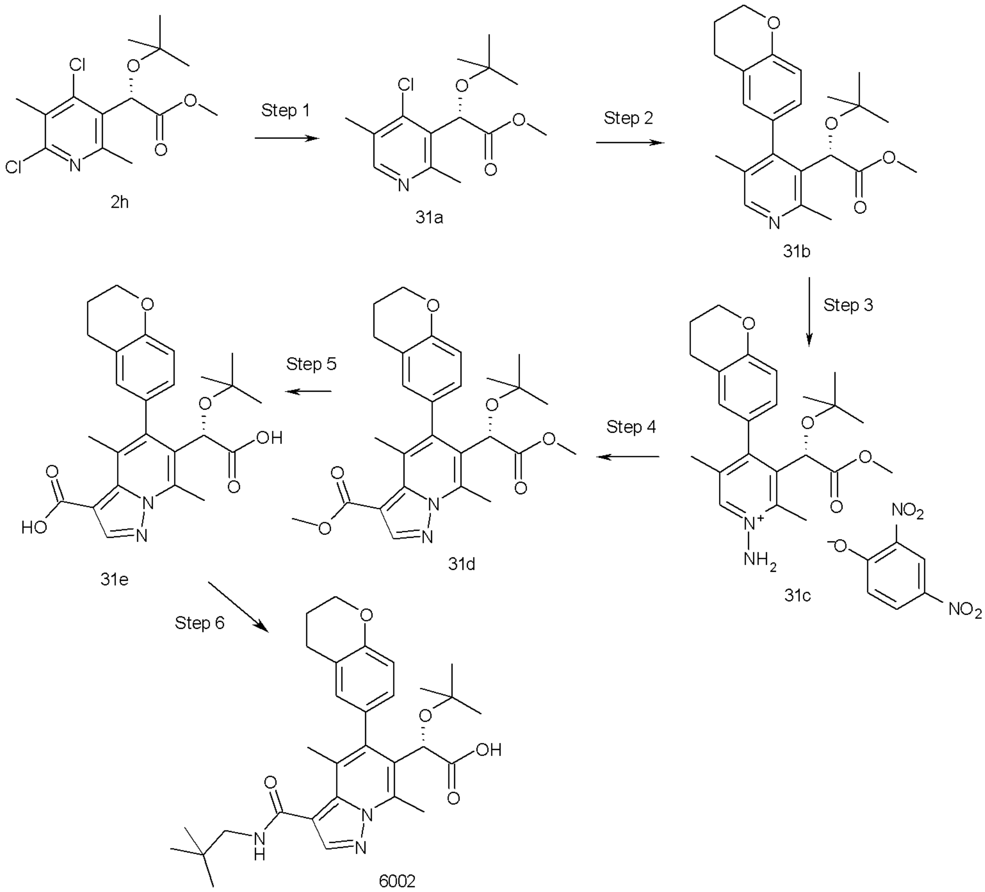
A mixture of **30c** (125 mg, 0.28 mmol) and DCM (1 mL) is treated with neopentylamine **29c** (Example 29) (65 μL, 0.55 mmol) and Et_3N (47 μL, 0.34 mmol), followed by addition of silver benzoate (16 mg, 0.07 mmol). The mixture is stirred at 23°C for 16 h. The mixture is diluted with DCM, washed with saturated NH_4Cl, saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated *in vacuo* providing **30d**.

Step 5:

A mixture of **30d** (40 mg, 0.08 mmol), chloroacetaldehyde (50% in water, 15 μL, 0.12 mmol) and $NaHCO_3$ (19.7 mg, 0.23 mmol) in EtOH (0.5 mL) is heated at reflux for 16 h. The mixture is cooled to 23°C and filtered, and the solvent is evaporated *in vacuo*. The residue is mixed with THF (1 mL) and MeOH (0.3 mL), and 1N NaOH (0.3 mL, 0.3 mmol) is added. The mixture is stirred at 45°C until the reaction is complete, then cooled to 23°C, adjusted to pH 5 with AcOH and purified by prep. HPLC to give compound **5002**.

EXAMPLE 31

SYNTHESIS OF COMPOUND 6002 (TABLE 6)



Step 1:

To a mixture of intermediate **2h** (Example 2) (5 g, 15.6 mmol) in AcOH (100 mL) is added zinc (15.3 g, 234 mmoles). The mixture is stirred at 60°C for 120 min, then is cooled to 23°C and filtered through a Celite® pad, and the filtrate is concentrated *in vacuo*. The residue is slowly neutralized with saturated $NaHCO_3$ and extracted twice with EtOAc. The organic layers are combined, washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the desired intermediate **31a**.

Step 2:

A mixture of DMA (15.8 mL) and distilled water (1.58 mL) is degassed for 10 min with nitrogen and added by syringe to a mixture of the intermediate **31a** (1 g, 3.5 mmol), 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-chroman **19d** (Example 19)

(1 g, 3.85 mmol) and $NaHCO_3$ (1.47 gr, 17.5 mmol) under nitrogen atmosphere in a 48 mL resealeable vessel equipped with a magnetic stirring bar and fixed with a rubber septum. Bis(tri-*t*-butylphosphine)palladium (179 mg, 0.35 mmol) is added to the reaction mixture and the vessel is placed in a sonicator for 10 min while being purged with nitrogen. The vessel is sealed with a Teflon cap and heated at 130°C for 4 h. The mixture is diluted with EtOAc and filtered through Celite®, and the organic extract is washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography (10-25-100% ethyl acetate: hexanes) affording **31b**.

Step 3:

To a 15 mL resealable vessel equipped with a magnetic stirring bar is added intermediate **31b** (500 mg, 1.3 mmol), *O*-(2,4-dinitrophenyl)hydroxylamine (300mg, 1.5 mmol; prepared as described in *Tet.Lett.* **1972**, *28*, 3833-3843) and MeCN (1.7 mL). The reaction vessel is sealed with Teflon cap and the mixture is stirred at 40ºC for 24 h, then is cooled to 23ºC and concentrated in vacuo affording **31c**.

Step 4:

To a mixture of **31c** (521 mg, 1.3 mmol) and DMF (17.4 mL) is added K_2CO_3 (198 mg, 1.43 mmol). The reaction mixture is stirred for 5 min at 23ºC (exposed to air), then methyl proprionate (132 mg, 1.56 mmol) is added and stirring is continued for 18 h. The mixture is diluted with EtOAC and washed with saturated $NaHCO_3$, water and brine. The organic layer is dried over$MgSO_4$, filtered and concentrated *in vacuo* and the residue is purified by flash chromatography (10-100% ethyl acetate: hexanes) affording **31d**.

Step 5:

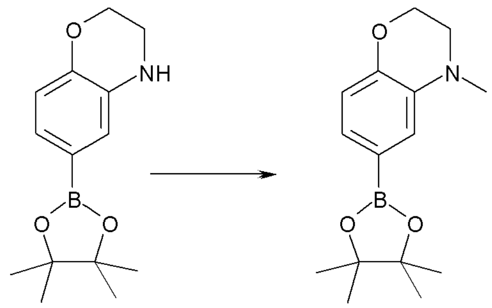
A mixture of **31d** (250 mg, 0.52 mmol), THF (2.5 mL) and MeOH (0.83 mL) is treated with a solution of 10 N NaOH (0.42 mL, 4.2 mmol) at 60ºC for 18 h. The mixture is adjusted to pH 1 with 1N HCl and extracted with DCM (3x). The combined organic layers are dried over $MgSO_4$, filtered and concentrated *in vacuo* affording intermediate **31e**.

Step 6:

Intermediate **31e** is transformed to compound **6002** using the procedure described in step 3 of Example 29.

EXAMPLE 32

SYNTHESIS OF INTERMEDIATE 32A

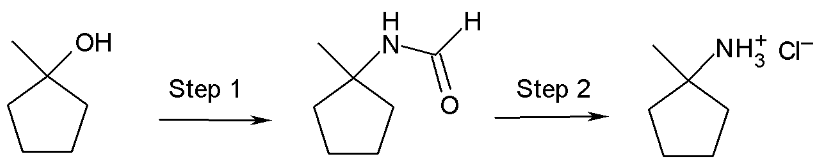


3h 32a

To a mixture of boronate **3h** (Example 3) (0.80 g, 3.1 mmol) and acetone (20 mL) is added K_2CO_3 (5.23 g, 38 mmol) followed by methyl iodide (2.9 mL, 39 mmol). The reaction vessel is sealed and the reaction mixture stirred at RT (24 h). The mixture is diluted with EtOAc and saturated brine. The aqueous phase is extracted with EtOAc (2x) and the combined organic phases are dried ($MgSO_4$), filtered and concentrated to dryness to afford the desired boronate **32a**.

EXAMPLE 33

SYNTHESIS OF INTERMEDIATE 33C



33a 33b 33c

Step 1:

To a mixture of methylcyclopentanol **33a** (2.0 g, 20 mmol) and AcOH (2.0 mL) is added KCN (1.43 g, 22 mmol) portionwise, followed by conc. H_2SO_4 (3.0 mL) added dropwise at a rate to keep the temperature at 30-35°C. The mixture is heated to 60°C for 30 min and is then stirred at RT (16 h). Ice water (35 mL) is added, and the mixture is adjusted to basic pH with solid K_2CO_3 and extracted with Et_2O (5x). The combined organic phases are dried over $MgSO_4$, filtered and concentrated to give **33b**.

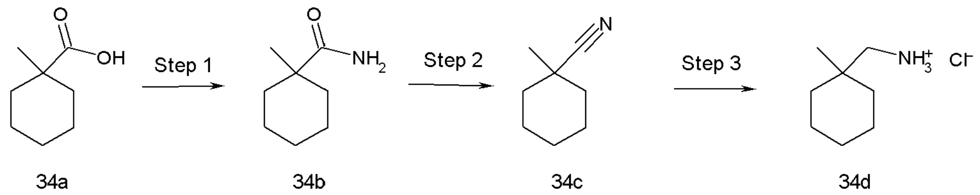
Step 2:

A mixture of derivative **33b** (1.5 g, 11.8 mmol) and dioxane (8 mL) is treated with 5N

HCl (8.0 mL) and EtOH (4 mL). The mixture is heated at gentle reflux for 4 h, then ethanol and dioxane are removed under vacuum. The aqueous phase is washed with hexanes and then concentrated. Traces of water are removed by azeotropic removal with EtOH. The resulting solid is dried under high vacuum to give the amine hydrochloride salt **33c**.

EXAMPLE 34

SYNTHESIS OF INTERMEDIATE 34D



Step 1:

A mixture of 1-methylcyclohexane carboxylic acid **34a** (25 g, 176 mmol) in DCM (125 mL) is cooled to 0°C and a catalytic amount of DMF (250 μL) is added. Oxalyl chloride (20 mL, 228 mmol) is then added dropwise over 30 min and the mixture is allowed to stir for 45 min. The reaction mixture is then warmed to RT and stirred an additional 2.5 h. The mixture is concentrated to dryness and dried and the residue is mixed with 1,4-dioxane (125 mL). To this mixture is added portionwise a solution of 20% ammonium hydroxide (125 mL) at RT (1 h). The mixture is diluted with water (200 mL) and extracted with EtOAc (3x). The combined organic extracts are washed with saturated brine, dried ($MgSO_4$), filtered and concentrated to give a crude solid. This material is dissolved in hot hexanes (125 mL) and left at 4°C (18 h). The solid formed is filtered and washed with cold hexanes to afford amide **34b**.

Step 2:

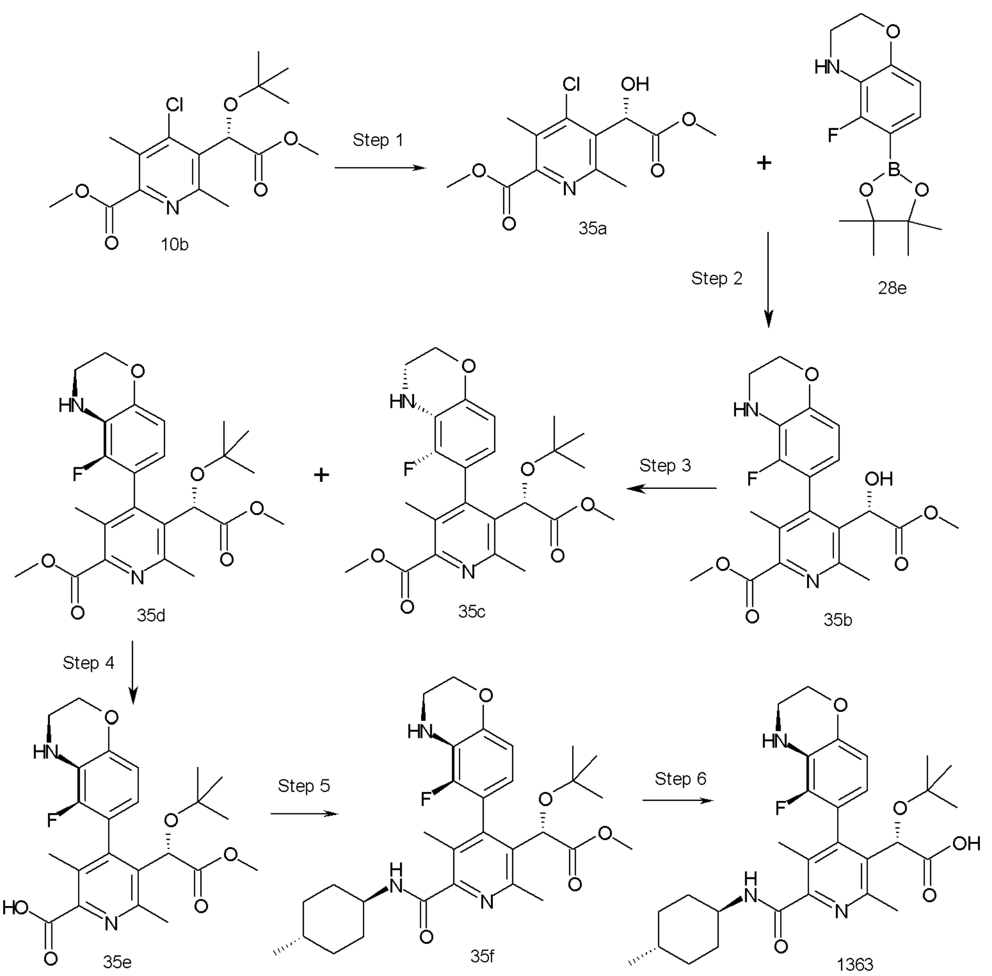
In a 2 necked round bottomed flask equipped with a condenser is added **34b** (18.0 g, 128 mmol) in thionyl chloride (12 mL, 106 mmol). The mixture is heated to reflux for 2 h until gas evolution ceases, then cooled to RT and diluted with Et_2O (125 mL) with careful addition of water (75 mL). The mixture is vigorously stirred for 5 min and then adjusted to basic pH with solid Na_2CO_3. The organic phase is separated and washed with saturated Na_2CO_3 and saturated brine, dried over $MgSO_4$, treated with charcoal and filtered through Celite®. The filtrate is concentrated under vacuum at RT to give **34c**.

Step 3:

To a mixture of EtOH (50 mL) and HCl (g) (8.3 g, 0.23 mmol) at 0°C is added **34c** (14.7 g, 119 mmol) followed by platinum oxide (400 mg). The mixture is placed in a Parr shaker and treated with H_2(g) at 40 psi for 48 h. The atmosphere is flushed and the mixture filtered through Celite® and washed with EtOH. The filtrate is concentrated to dryness and the residue is washed with ether, filtered and dried to give the intermediate **34d** as the hydrochloride salt.

EXAMPLE 35

SYNTHESIS OF COMPOUND 1363 (TABLE 1) INCLUDING SEPARATION OF ATROPISOMERS



Step 1:

To a mixture of the diester **10b** (1.0g, 2.91 mmol), DCM (7 mL) and MeOH (0.25 mL) is added TFA (8 mL). The mixture is allowed to stir at RT for 2 h and is concentrated to dryness. The residue is taken up in EtOAc and washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to give alcohol **35a**.

Step 2:

A mixture of boronate **28e** (400 mg, 1.43 mmol), alcohol **35a** (420 mg, 1.46 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos, 59 mg, 0.1 mmol), tris(dibenzylideneacetone)dipalladium(0) (39 mg, 0.04 mmol) and Na_2CO_3 (607 mg, 5.7 mmol) in 2-methyl tetrahydrofuran (5.6 mL) and water (1.4 mL) is placed in a sealable vessel. The mixture is degassed by bubbling argon through the solution (10 min) and the vessel is sealed and heated at 75°C (20 h). Further portions of the catalyst and ligand are added and the mixture is again heated at 75°C (20 h). The cooled mixture is filtered, diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue is purified by CombiFlash® Companion to give a mixture of isomers **35b**.

Step 3:

The mixture of alcohols **35b** (362 mg, 0.90 mmol) in tert-butyl acetate (7.1 mL, 53 mmol) is cooled to 0°C in an ice bath and treated portionwise with perchloric acid (70% w/w in water, 1.2 mL, 13.4 mmol). The vessel is capped and the reaction mixture stirred at 0°C until about 50% completion. The reaction is quenched with 1N NaOH (pH~9) and the mixture is extracted with EtOAc. The organic phase is washed with water and brine, dried over Na_2SO_4 and concentrated. The residue is purified by CombiFlash® Companion (20 to 100% EtOAc/hexanes) to give the separated isomers **35c** and **35d** plus unreacted starting alcohols **35b**.

Step 4:

To a mixture of diester **35d** (87 mg, 0.19 mmol), MeOH (0.4 mL) and THF (1.2 mL) is added 1N LiOH (0.21 mL, 0.21 mmol). The mixture is allowed to stir at RT (16 h) then is acidified with 1N HCl and extracted with EtOAc (2x). The organic extract is dried over Na_2SO_4, filtered and concentrated to give acid **35e**.

Step 5:

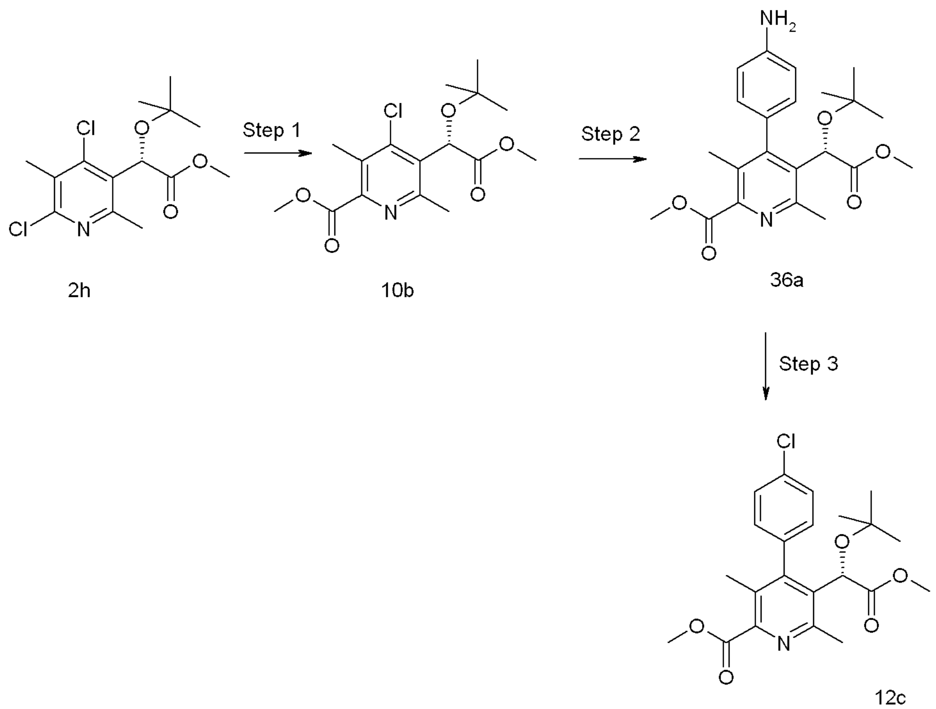
A mixture of acid **35e** (30 mg, 0.06 mmol) and NMP (1 mL) is treated with TBTU (40 mg, 0.12 mmol) and Et_3N (35 μL, 0.25 mmol). The mixture is allowed to stir at RT for 5 min then trans-4-methylcyclohexyl amine (25 μL, 0.19 mmol) is added. The reaction is allowed to stir at RT (2 h) and is then diluted with EtOAc. The organic phase is washed with saturated NH_4Cl, H_2O, and brine, dried over $MgSO_4$, filtered and concentrated to dryness to afford the amide **35f**.

Step 6:

A mixture of amide **35f**, THF (0.9 mL) and MeOH (0.3 mL) is treated with 1N NaOH (0.29 ml, 0.29 mmol) at 50°C (1 h). The solution is acidified with AcOH and purified by preparative HPLC. The pure fractions are combined, concentrated to remove MeCN and then extracted into DCM. The organic phase is dried over Na_2SO_4, filtered and concentrated. This solid is re-dissolved in DCM and treated with 10 drops of 1N NaOH and then neutralized with AcOH. The phases are separated and the aqueous layer is extracted with DCM. The combined organic phases are concentrated and lyophilized to give compound **1363**.

EXAMPLE 36

ALTERNATIVE SYNTHESIS OF INTERMEDIATE 12C



Step 1:

A steel bomb is charged with the compound **2h** (11 g, 34.3 mmol), $Pd(OAc)_2$ (0.17 mg, 0.68 mmol) , bis(diphenylphosphino)ferrocene (0.42 g, 0.76 mmol) and 2,6-lutidine (8.0 mL, 68.7 mmol). Degassed MeOH (50 mL) is added and the system is sealed. The system is purged with N_2 (2x) and CO (3x). The mixture is stirred at 110°C under 200 psi of CO for 48 h. The reaction mixture is filtered, concentrated and purified by Combiflash® Companion to give **10b**.

Step 2:

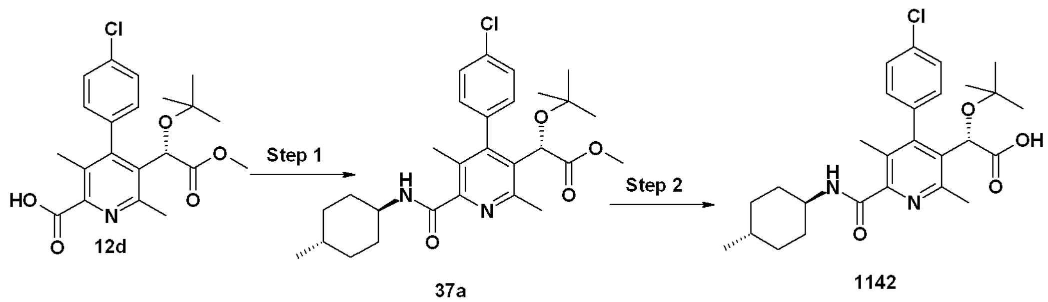
Intermediate **10b** is transformed to intermediate **36a** using the procedure described in step 1 of Example 12.

Step 3:

Intermediate **36a** is transformed to intermediate **12c** using the procedure described in step 2 of Example 5.

EXAMPLE 37

SYNTHESIS OF COMPOUND 1142 (TABLE 1)



Step 1:

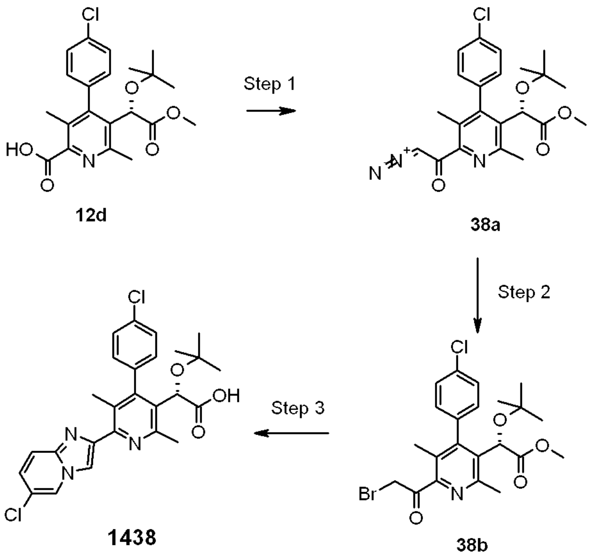
Intermediate **12d** is transformed to intermediate **37a** using the procedure described in step 5 of Example 35.

Step 2:

A mixture of amide **37a**, (30 mg, 0.06 mmol), THF (2.5 mL) and MeOH (0.75 mL) is treated with 5N NaOH (65 µL, 0.33 mmol) at 60°C (1 h). The solution is neutralized with AcOH (19 µL, 0.33 mmol) and evaporated to dryness. The residue is then purified by CombiFlash® Companion to give compound **1142**.

EXAMPLE 38

SYNTHESIS OF COMPOUND **1438** (TABLE **1**)



Step 1:

To **12d** (1 g, 2.5 mmol) and Et_3N (481 µL, 3.5 mmol) in THF (13 mL) at 0°C is added isobutyl chloroformate (448 µL, 3.5 mmol) dropwise. The mixture is stirred at 0°C for 1 h. A diazomethane solution (0.67 M in diethyl ether, 37 mL, 25 mmol) is added slowly and the mixture is allowed to reach 23°C. After 1 h, the mixture is concentrated *in vacuo* and then EtOAc and water are added. The organic layer is washed with a saturated aqueous solution of $NaHCO_3$, water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Crude product is is purified by CombiFlash® Companion to give **38a**.

Step 2:

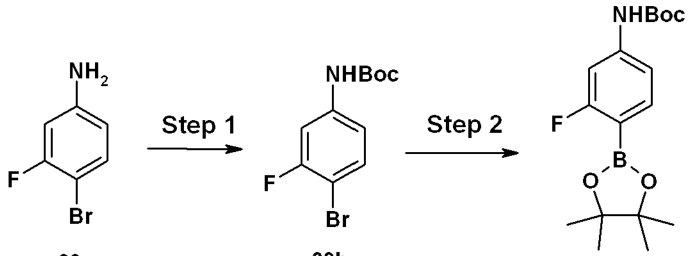
To a solution of **38a** (828 mg, 2.5 mmol) in THF (16 mL) at 0°C is added dropwise an HBr solution (48% aq, 1.09 mL, 9.6 mmol). The mixture is stirred for 1 h at 0°C.The solution is diluted with EtOAc, washed with $NaHCO_3$ (sat), water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide **38b**.

Step 3:

To **38b** (50 mg, 0.1 mmol) in a mixture of EtOH (750 µL) and acetone (150 µL) is added $NaHCO_3$ (8.1 mg, 0.11 mmol) and 2-amino-5-chloropyridine (14.7 mg, 0.11 mmol) in a sealed tube. The mixture is heated at 85°C for 30 min then concentrated *in vacuo*. The residue is diluted with THF (1 mL), MeOH (300 µL) and a NaOH solution (5 N, 103 µL, 0.52 mmol) and the resulting mixture is then stirred for 15 min at 60°C. The mixture is cooled to 23°C and the pH is adjusted to ~5-6 with AcOH. The crude mixture is purified by prep HPLC (MeOH/water containing 10mM ammonium bicarbonate (pH10)). The desired fractions are collected and concentrated under reduced pressure. The residue is dissolved in MeCN (1.5 mL) and freeze-dried to give **1438**.

EXAMPLE 39

SYNTHESIS OF INTERMEDIATE 39C



39a 39b 39c

Step 1:

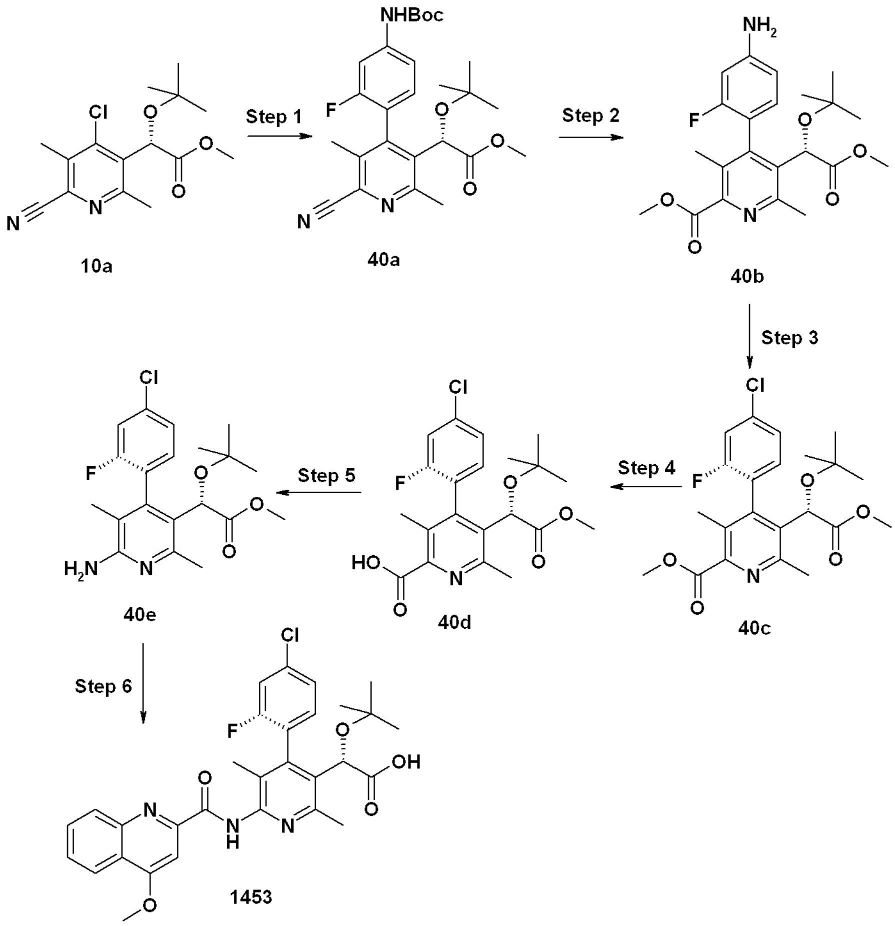
To a THF solution (90 mL) of **39a** (7.2 g, 38 mmol) is added solid $NaHCO_3$ (16 g, 190 mmol) and water (9 mL) at RT. This mixture is stirred for 10 min before the portionwise addition of solid di-t-butyl dicarbonate (16.5 g, 76 mmol). The mixture is stirred at 55°C for 16 h or until completion. The mixture is filtered and then partitioned between EtOAc and water. The aqueous phase is extracted with EtOAc and the combined organic phases are washed with brine, dried ($MgSO_4$) filtered and concentrated. The crude product is purified by CombiFlash® Companion to give **39b**.

Step 2:

To **39b** (11 g, 37.8 mmol) dissolved in dry 1,4-dioxane (120 mL) is added bis(pinacolato)diboron (13.7 g, 54 mmol) and potassium acetate (9.9 g, 101 mmol) before being deoxygenated by bubbling a stream of argon for 15 min. To this mixture is added 1,1'-bis(diphenylphosphino)ferrocene (2.75 g, 3.4 mmol). This mixture is degassed a further 5 min before being refluxed at 100°C for 16 h. The cooled mixture is diluted with EtOAc and water and then filtered through Celite. The phases are separated and the organic layer is washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The resulting residue is purified by CombiFlash® Companion to give intermediate **39c**.

EXAMPLE 40

SYNTHESIS OF COMPOUND 1453 (TABLE 1)



Step 1:

Intermediate **10a** (4.0 g, 12.9 mmol) is treated with boronate **39c** (5.2 g, 15.5 mmol) using the procedure described in step 1 of Example 12 to afford **40a**.

Step 2:

Intermediate **40a** is transformed to diester **40b** using the procedure described in step 3 of Example 12.

Step 3:

Aniline **40b** (2.86 g, 6.84 mmol) is converted to intermediate **40c** using the procedure described in step 2 of Example 5. The atropisomers are separated at this stage by CombiFlash® Companion to give **40c**.

Step 4:

Diester **40c** is converted to mono-acid **40d** using the procedure described in step 4 of Example 12.

Step 5:

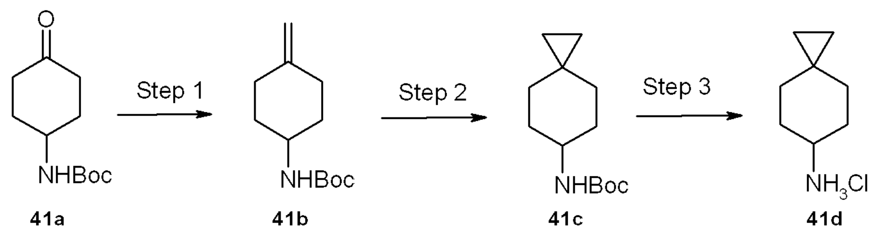
Intermediate **40d** is transformed to intermediate **40e** using the procedure described in step 5 of Example 12.

Step 6:

To a solution of 4-methoxy-2-quinoline carboxylic acid (302 mg, 1.5 mmol) and DMF (15 μL) in DCM (7 mL) is added oxalyl chloride as a 2M solution in DCM (968 μL, 1.94 mmol) dropwise at RT (with evolution of gas). After 20 min, the solution is concentrated to dryness and then dissolved in THF (2 mL). To this solution is added intermediate **40e** (294 mg, 0.74 mmol) and DIPEA (650 μL, 3.72 mmol) then heated at 50°C for 2h. The cooled reaction mixture is diluted with EtOAC and washed consecutively with a NH_4Cl solution (sat), a $NaHCO_3$ solution (sat) and brine. The organic phase is dried ($MgSO_4$), filtered and concentrated to dryness. The solution of the crude ester (431 mg, 0.74 mmol) in THF (4 mL) and MeOH (2 mL) is heated at 50°C before being treated with 5 N NaOH (743 μL, 3.72 mmol). The reaction is stopped after 1 h by quenching with AcOH (500 μL) and the mixture is concentrated to dryness. The residue is taken up into MeOH and purified by preparative HPLC to give, after lyophilization, compound **1453**.

EXAMPLE 41

SYNTHESIS OF INTERMEDIATE 41D



Step 1:

Compound **41a** is converted to **41b** using dimsyl sodium and methyl-triphenylphosphoium bromide as described in J. Am. Chem. Soc., **1980**, *102*, 1404-1408.

Step 2:

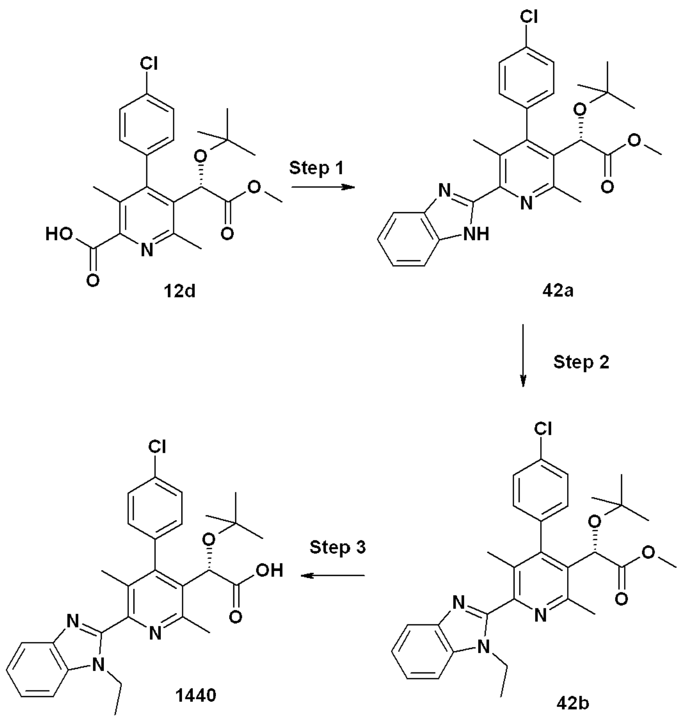
Intermediate **41b** (250 mg, 1.18 mmol) is dissolved in diethyl ether (5 mL) and cooled to 0°C before being treated with diazomethane in ether (40 mL, 2.8 mmol). To this cooled solution is added portionwise palladium (II) acetate (5 x 5 mg). This sequence is repeated until the reaction is complete by NMR analysis. The solution is filtered and concentrated to give **41c**.

Step 3:

To **41c** (261 mg, 1.16 mmol) is added 4M HCl/dioxane (5 mL, 20 mmol) and the mixture is allowed to stir at RT for 2 h. The solution is concentrated and then treated with diethyl ether. This mixture is sonicated to afford a solid which is filtered and dried to give **41d** as the HCl salt.

EXAMPLE 42

SYNTHESIS OF COMPOUND 1440 (TABLE 1)



Step 1:

A solution of 2-aminoaniline (27 mg, 0.25 mmol), HATU (110 mg, 0.30 mmol) and **12d** (0.10 g, 0.25 mmol) in DMF (3 mL) at RT is treated with Et_3N (0.10 mL, 0.74 mmol). This mixture is stirred at RT for 1 h. EtOAc (10 mL) is added and the solution is washed with brine, dried ($MgSO_4$), filtered and the solvent evaporated. The crude amide is dissolved in AcOH (4 mL) and heated at 80^0C (1 h). The solution is concentrated, EtOAc (10 mL) is added and the solution is washed with saturated $NaHCO_3$ and brine. The layers are separated and the organic layer is evaporated to give the crude benzimidazole. The product is purified by CombiFlash® Companion to afford **42a**.

Step 2:

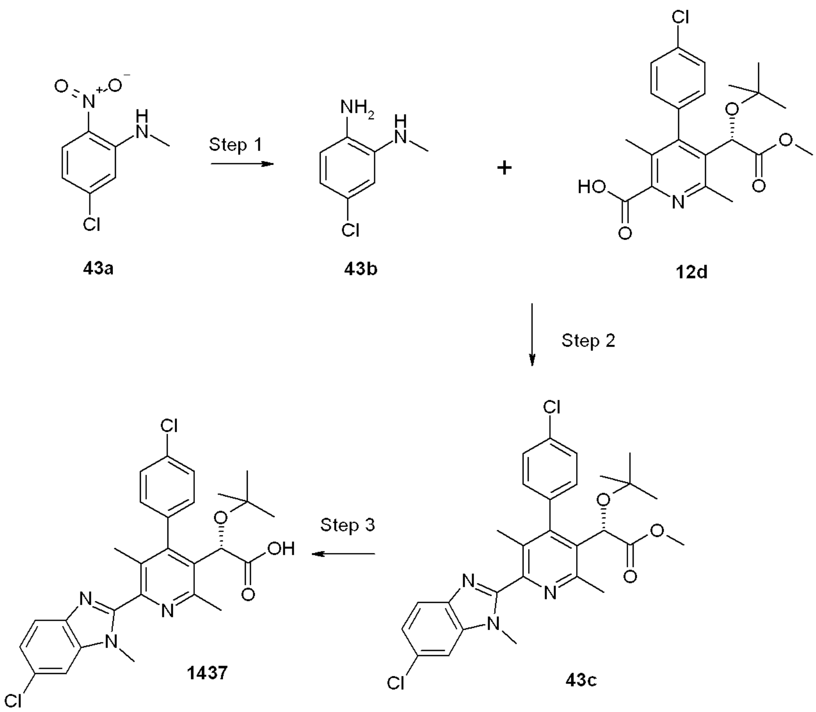
A solution of benzimidazole **42a** (120 mg, 0.25 mmol) in DMF (1.5 mL) is treated with NaH (60% dispersion in mineral oil, 11 mg, 0.27 mmol) and the mixture is stirred for 15 min. Iodoethane (30 µL, 0.37 mmol) is added and the reaction is stirred for 1 h. The reaction is diluted with water (15 mL) and extracted with EtOAc (15 mL). The organic layer is dried ($MgSO_4$) and evaporated to dryness to give compound **42b.**

Step 3:

A mixture of amide **42b** (125 mg, 0.25 mmol) in THF (3.5 mL) and MeOH (0.5 mL) is treated with 5N NaOH (250 µL, 1.5 mmol) at 50°C (3 h). The solution is acidified with AcOH and evaporated to dryness. The residue is then dissolved in MeOH (1 mL) and purified by preparative HPLC. The fractions containing pure compound are pooled, evaporated to dryness, redissolved in 1:1 MeCN / water (50 mL), frozen and lyophilized to give compound **1440**.

EXAMPLE 43

SYNTHESIS OF COMPOUND 1437 (TABLE 1)



Step 1:

To a solution of compound **43a** (1.9 g, 10 mmol) in THF is added tin powder and 1N

HCl (50 mL, 50 mmol). After 1 h of vigorous stirring, 1 N NaOH (50 mL) is added slowly to the reaction. The mixture is filtered on Celite and the filter cake is washed with EtOAc (200 mL). The filtrate is extracted with EtOAc and the combined organic layers are dried (Na_2SO_4) and concentrated to dryness to give compound **43b**.

Step 2:

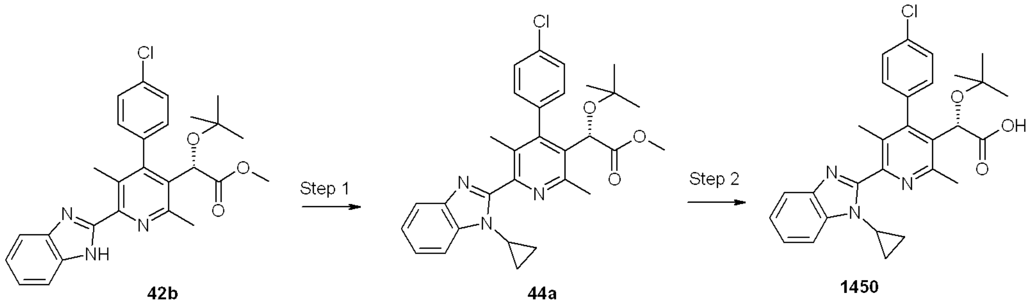
Intermediates **43b** and **12d** are coupled to give intermediate **43c** using the procedure described in step 1 of Example 42.

Step 3:

Intermediate **43c** is transformed to compound **1437** using the procedure described in step 3 of Example 42.

EXAMPLE 44

SYNTHESIS OF COMPOUND 1450 (TABLE 1)



42b 44a 1450

Step 1:

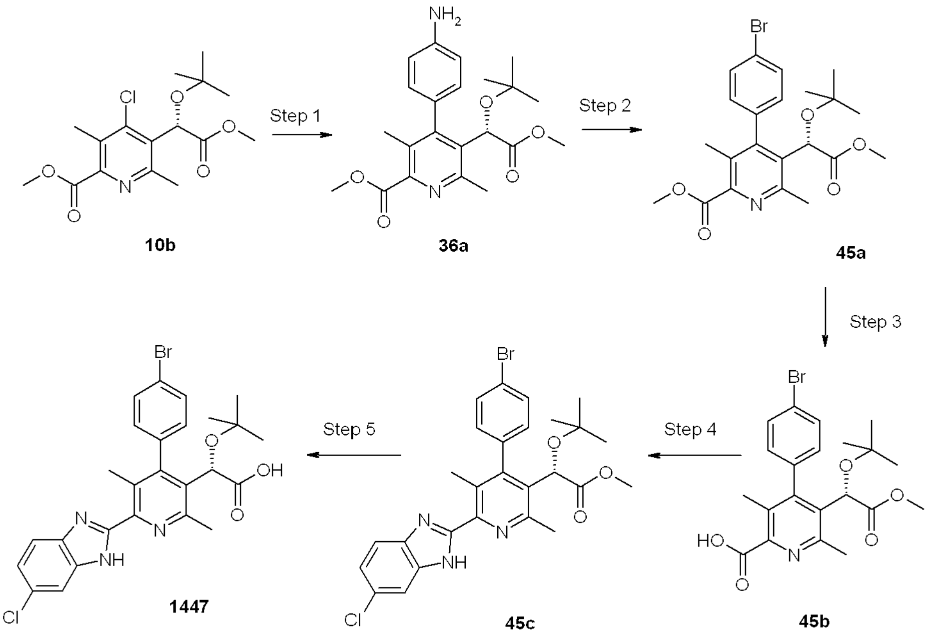
A mixture of benzimidazole **42b** (88 mg, 0.19 mmol), cyclopropyl boronic acid (32 mg, 0.37 mmol), copper acetate (34 mg, 0.19 mmol) 2,2-bipyridyl (29 mg, 0.19 mmol) and Na_2CO_3 (39 mg, 0.37 mmol) in DCE (3 ml) is heated to 70 °C for 18 h. The mixture is cooled to RT and washed with a mixture of water / saturated NH_4Cl (15 mL each). The water layer is extracted with DCM, and the organic layer is washed with brine, dried ($MgSO_4$), filtered and concentrated to give compound **44a**.

Step 2:

Intermediate **44a** is transformed to compound **1450** using the procedure described in step 3 of Example 42.

EXAMPLE 45

SYNTHESIS OF COMPOUND 1447 (TABLE 1)



<u>Step 1:</u>

Intermediate **10b** is transformed to intermediate **36a** using the procedure described in step 1 of Example 12

<u>Step 2:</u>

t-Butyl nitrite (90% w/w, 1.0 mL, 7.9 mmol) is added to a stirred suspension of $CuBr_2$ (1.6 g, 7.3 mmol) in anhydrous, deoxygenated MeCN (12 mL) cooled to 0°C under a nitrogen atmosphere. A solution of compound **36a** in dry, deoxygenated MeCN (15 mL + 5 mL rinse) is added dropwise and the reaction is allowed to warm to RT. After 4 h, additional t-butyl nitrite (0.3 mL, 2.4 mmol) is added and the stirring is continued. After 16 h, silica gel is added (30 g) and the solvent is evaporated. The product is purified by CombiFlash® Companion to afford intermediate **45a**.

<u>Step 3:</u>

Intermediate **45a** is transformed to intermediate **45b** using the procedure described in step 4 of Example 12.

<u>Step 4:</u>

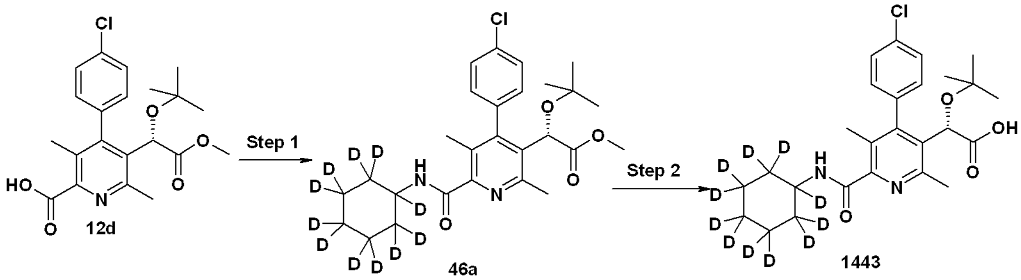
Intermediate **45c** is transformed to intermediate **45c** using the procedure described in step 1 of Example 42.

<u>Step 5:</u>

Intermediate **45c** is transformed to intermediate **1447** using the procedure described in step 3 of Example 42.

EXAMPLE 46

SYNTHESIS OF COMPOUND 1443 (TABLE 1)



Step 1:

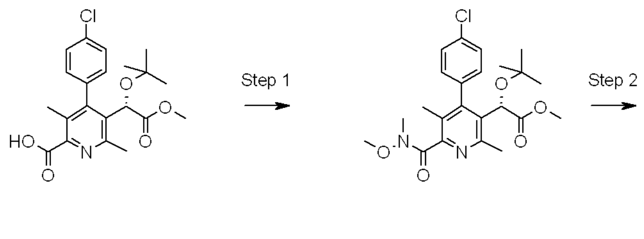
Intermediate **12d** and commercially available D-11 cyclohexylamine (CDN Isotopes) are coupled to give intermediate **46a** using the procedure described in step 5 of Example 35.

Step 2:

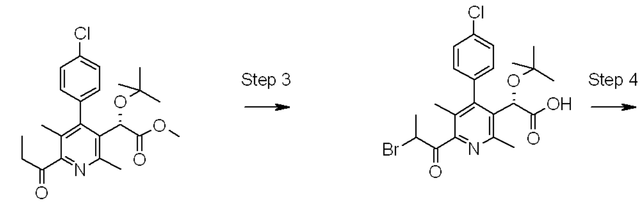
Intermediate **46a** is transformed to compound **1443** using the procedure described in step 2 of Example 37.

EXAMPLE 47

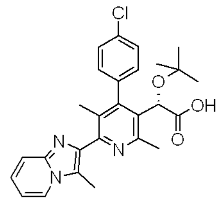
SYNTHESIS OF COMPOUND 1470 (TABLE 1)



12d 47a



47b 47c



1470

Step 1:

To **12d** (200 mg, 0.49 mmol) in *N*-methylpyrrolidinone (2.5 mL) is added Et_3N (137 µL, 0.99 mmol) followed by N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (320 mg, 0.99 mmol). The mixture is stirred for 10 min, treated with *N,O*-dimethylhydroxylamine hydrochloride (96 mg, 0.99 mmol) and then stirred for 60 h at 23°C. A saturated, aqueous solution of ammonium chloride is added to the mixture. The solution is diluted with water and extracted with EtOAc (2x). The combined organic layers are washed with water (2x), brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product is purified by CombiFlash® Companion with an eluting gradient of 20 to 100% EtOAc / hexanes to afford **47a**.

Step 2:

To a solution of **47a** (163 mg, 0.36 mmol) in THF (3.6 mL) at -78°C is added dropwise an ethyl magnesium bromide solution (2.2 M in THF, 198 µL, 0.44 mmol). The mixture is stirred for 30 min at -40°C. A 1N HCl solution (~10-15 mL) is added to the reaction mixture and then the mixture is extracted with diethyl ether (2x). The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product is purified by CombiFlash® Companion with an eluting gradient of 5 to 20% EtOAc / hexanes affording pure **47b**.

Step 3:

To **47b** (100 mg, 0.24 mmol) in THF (1 mL) is added phenyl trimethylammonium tribromide (94.5 mg, 0.25 mmol). The reaction mixture is stirred at reflux for 20 h. The solution is taken up in EtOAc, washed with $NaHCO_3$ (sat), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **47c**.

Step 4:

To **47c** (50 mg, 0.1 mmol) in a mixture of EtOH (729 μL) and acetone (145 μL) is added $NaHCO_3$ (8.8 mg, 0.11 mmol) and 2-aminopyridine (14.2 mg, 0.11 mmol) in a resealable tube. The mixture is heated at 85°C for 2 h then concentrated *in vacuo*. The residue is diluted with THF (1 mL), MeOH (300 μL), aqueous NaOH solution (5N, 140 μL, 0.70 mmol) and stirred for 60 h at 23°C. The pH of the mixture is adjusted to approximately 5-6 with AcOH. The crude mixture is purified by prep HPLC (MeOH: water containing 10mM ammonium formate (pH 3.8)). The desired fractions are collected and concentrated under reduced pressure. The residues are dissolved in AcCN (1.5 mL) and freeze-dried to afford **1470**.

EXAMPLE 48

C8166 HIV-1 LUCIFERASE ASSAY (EC_{50})

C8166 cells are derived from a human T-lymphotrophic virus type 1 immortalized but nonexpressing line of cord blood lymphocytes (obtained from J. Sullivan and originally produced in the laboratory of R. Gallo, Virology 1983; 129: 51-64) 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 is selected by 3 consecutive rounds of limiting dilution under blasticidine selection. Cultures are maintained in complete media (consisting of: Roswell Park Memorial Institute medium (RPMI) 1640 + 10% FBS + 10^{-5} M β-mercaptoethanol + 10 μg/ml gentamycin) with 5 μg/ml blasticidine, however, blasticidine selection is removed from the cells before performing the viral replication assay.

LUCIFERASE ASSAY PROTOCOL

Preparation of Compounds

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

Infection of Cells

C8166 LTRluc cells are counted and placed in a minimal volume of complete RPMI 1640 in a tissue culture flask (ex. 30 X 10^6 cells in 10 mL media/25 cm^2 flask). Cells are infected with HIV-1 or virus with variant integrase generated as described below at a molecules of infection (moi) of 0.005. Cells are incubated for 1.5 hours at 37°C on a rotating rack in a 5% CO_2 incubator and re-suspended in complete RPMI to give a final concentration of 25,000-cells/175 µL. 175 µL of cell mix is added to wells of a 96 well microtiter plate containing 25 µL 8X inhibitors. 25,000 uninfected C8166-LTRluc cells/well in 200 µL complete RPMI are added to the last row for background control. Cells are incubated at 37 °C in 5% CO_2 incubator for 3 days.

Luciferase Assay

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

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

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

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

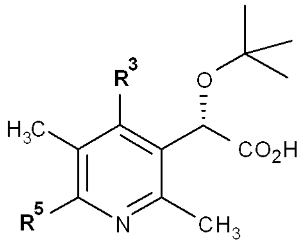
$$\% \cdot inhibition = \frac{I_{\max} \times [inhibitor]^n}{[inhibitor]^n + IC_{50}{}^n}$$

All compounds of Tables 1 to 6 have EC_{50} values of 500 nM or less against the NL4.3 strain of HIV-1 integrase (SEQ ID NO: 1) as measured by the assay of Example 48. The potency of representative compounds is provided in Table 7.

TABLES OF COMPOUNDS

The following tables list compounds of the invention. Compounds of the invention are particularly effective at inhibiting HIV integrase. Retention times (t_R) for each compound are measured using the standard analytical HPLC or, where indicated, UPLC 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 or UPLC instruments. Even when measured on the same instrument, the values may vary when measured, for example, using different individual HPLC or UPLC 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.

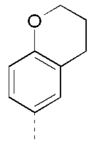
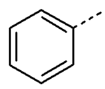
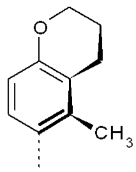
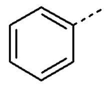
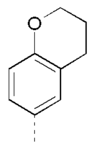
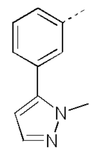
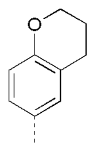
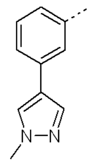
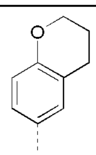
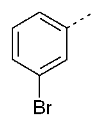
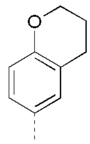
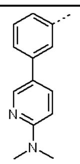
TABLE 1

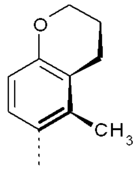
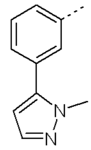
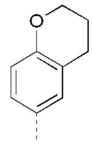
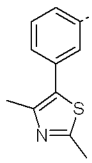
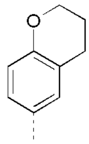
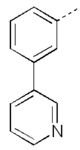
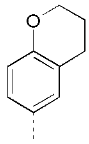
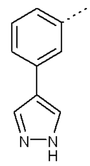
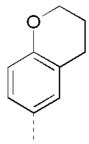
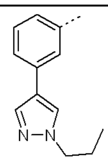
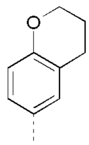
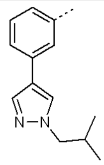
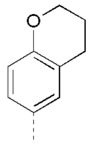
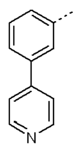
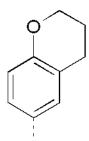
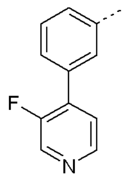
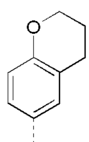
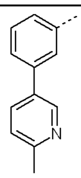


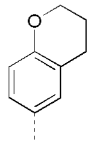
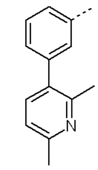
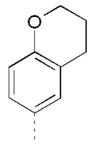
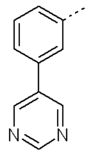
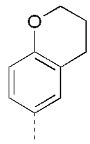
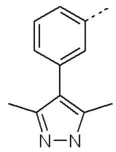
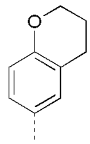
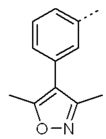
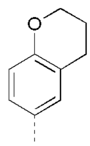
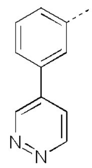
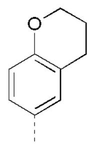
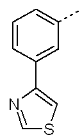
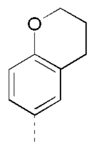
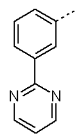
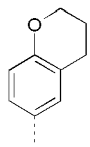
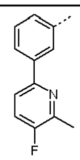
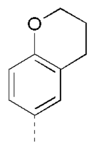
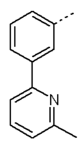
*presence of 2 inter-converting conformers by HPLC

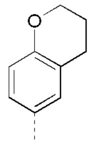
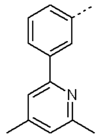
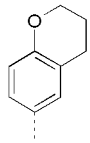
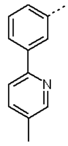
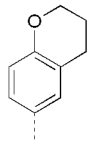
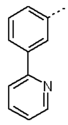
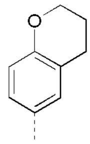
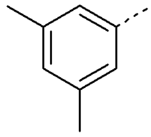
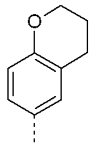
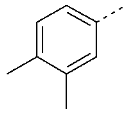
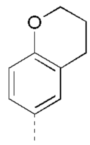
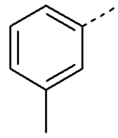
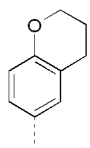
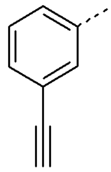
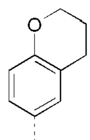
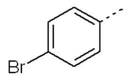
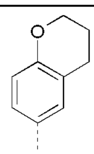
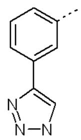
**Most active atropisomer

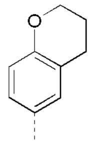
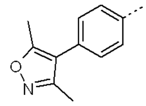
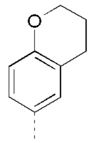
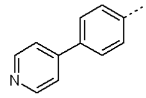
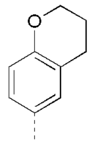
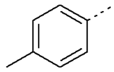
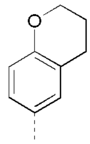
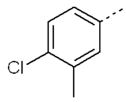
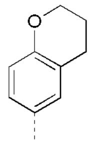
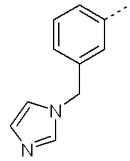
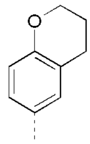
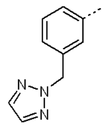
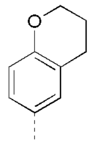
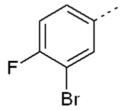
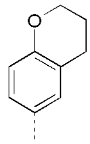
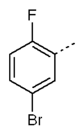
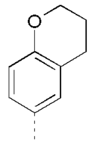
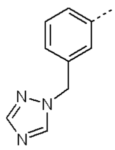
$Retention time ($t_R$) measured by UPLC

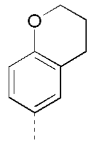
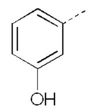
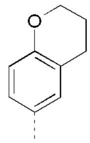
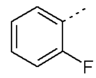
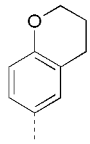
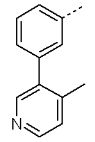
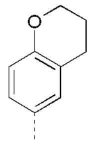
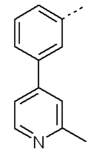
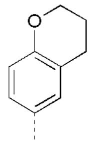
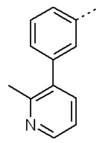
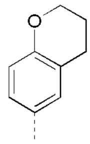
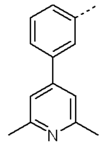
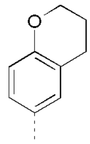
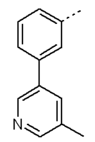
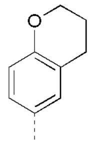
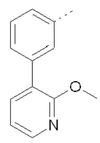
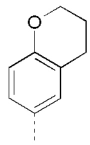
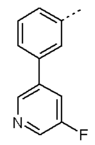
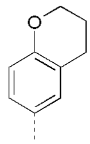
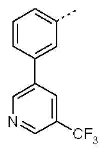
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1001			5.0/5.1 *	446.2
1002			5.2**	460.3
1003			4.9/5.0 *	526.3
1004			4.9/5.0 *	526.3
1005			5.4/5.5 *	524.1 526.1
1006			4.3/4.4 *	566.3

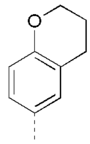
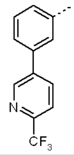
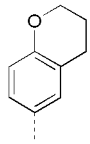
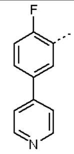
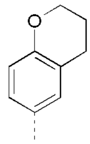
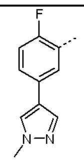
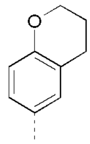
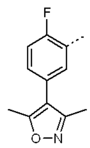
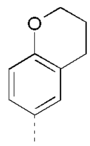
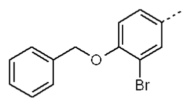
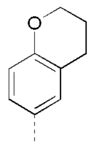
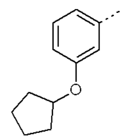
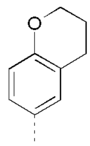
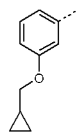
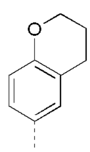
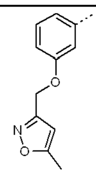
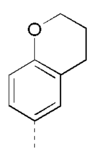
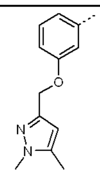
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1007			3.6	540.2
1008			3.4	557.2
1009			3.0	523.2
1010			4.8	512.2
1011			5.5	554.3
1012			5.8	568.3
1013			4.2	523.2
1014			4.8	541.2
1015			4.1/4.2 *	537.3

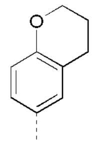
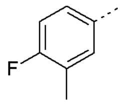
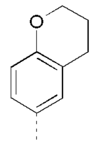
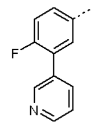
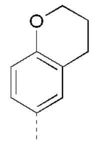
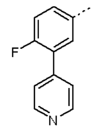
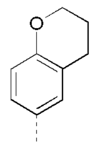
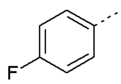
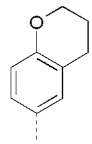
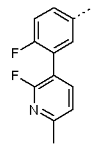
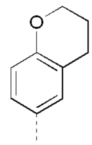
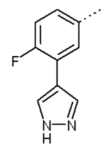
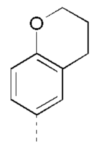
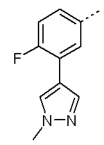
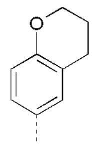
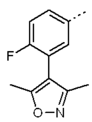
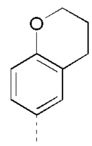
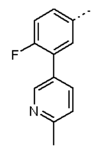
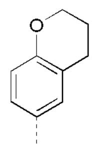
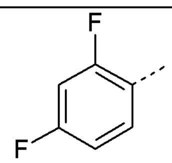
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1016			4.2	551.2
1017			4.7/4.8 *	524.0
1018			4.5	540.2
1019			5.4	541.2
1020			4.5/4.6 *	524.2
1021			5.2/5.3 *	529.2
1022			5.0/5.1 *	524.2
1023			5.7/5.8 *	555.2
1024			4.2/4.3 *	537.2

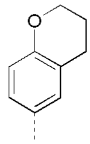
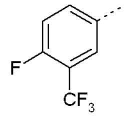
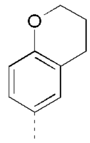
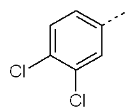
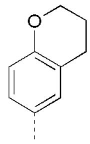
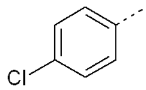
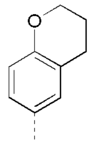
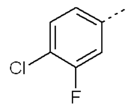
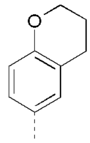
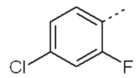
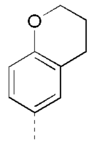
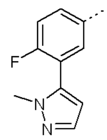
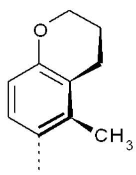
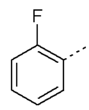
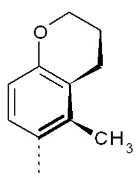
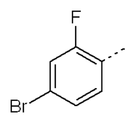
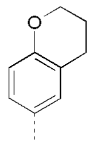
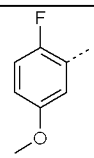
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1025			4.2/4.3 *	551.3
1026			4.3/4.4 *	537.2
1027			4.3/4.4 *	523.2
1028			5.5/5.6 *	474.2
1029			5.5/5.6 *	474.2
1030			5.3/5.4 *	460.1
1031			5.3/5.4 *	470.3
1032			5.4/5.5 *	524.2/ 526.2
1033			4.7/4.8 *	513.3

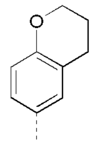
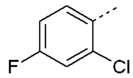
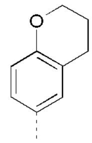
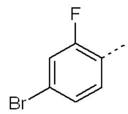
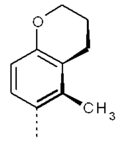
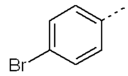
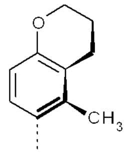
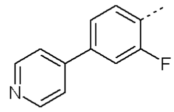
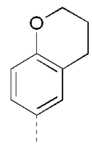
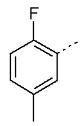
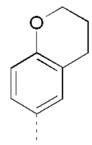
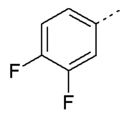
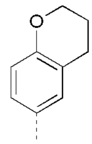
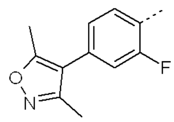
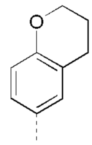
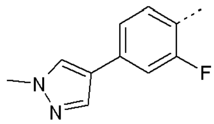
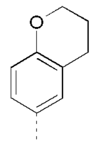
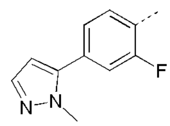
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1034			5.3/5.4 *	541.4
1035			4.0/4.1 *	523.4
1036			5.4	460.4
1037			5.7	494.3 496.3
1038			4.0	526.3
1039			5.0	527.3
1040			5.5/5.6 *	542.1/ 544.1
1041			5.6/5.7 *	542.1/ 544.1
1042			4.5	527.4

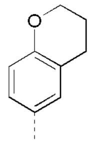
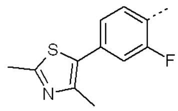
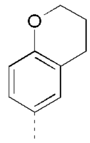
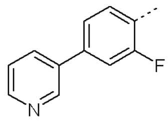
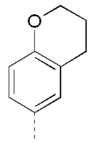
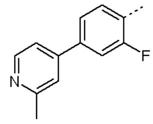
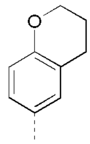
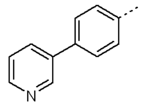
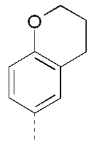
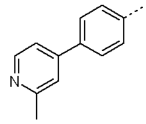
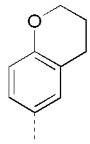
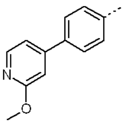
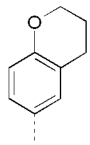
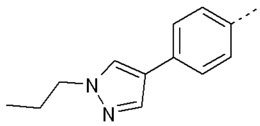
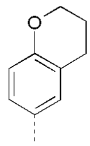
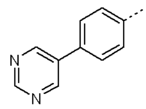
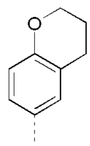
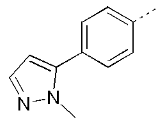
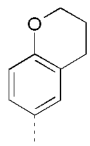
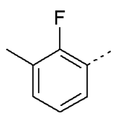
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1043			3.4	462.3
1044			5.0	464.3
1045			4.1/4.2 *	537.3
1046			4.2	537.3
1047			4.1/4.2 *	537.3
1048			4.2/4.3 *	551.3
1049			4.2/4.3 *	537.3
1050			5.4/5.5 *	553.3
1051			5.1/5.2 *	541.3
1052			5.7	591.3

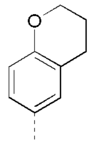
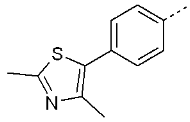
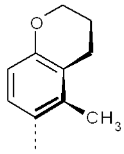
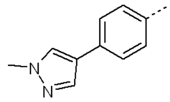
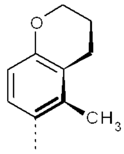
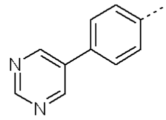
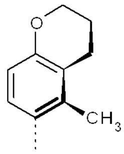
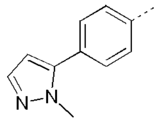
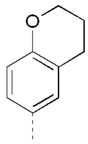
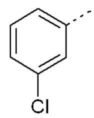
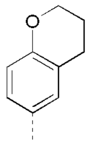
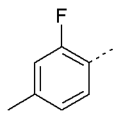
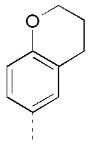
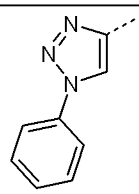
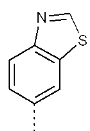
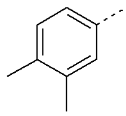
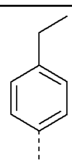
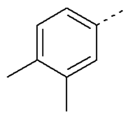
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1053			5.8	591.3
1054			4.3	541.3
1055			5.1/5.2 *	544.3
1056			5.4/5.5 *	559.3
1057			6.2	630.2/ 632.2
1058			6.0	530.3
1059			5.6	516.3
1060			5.3	557.3
1061			5.0	570.3

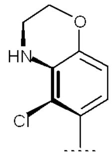
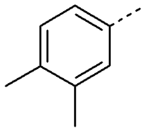
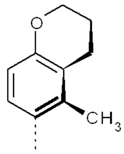
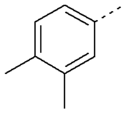
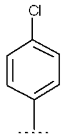
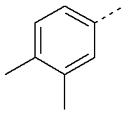
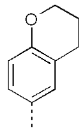
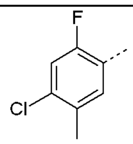
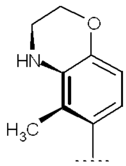
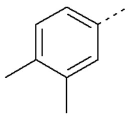
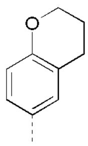
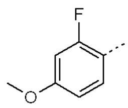
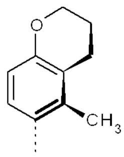
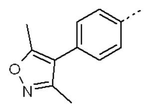
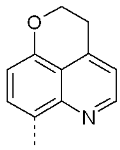
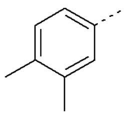
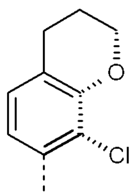
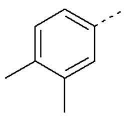
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1062			5.3/5.4 *	478.3
1063			4.3	541.3
1064			4.1/4.2 *	541.3
1065			5.1/5.2 *	464.3
1066			5.5/5.6 *	573.3
1067			4.9/5.0 *	530.3
1068			5.1/5.2 *	544.3
1069			5.4/5.5 *	559.3
1070			4.3	555.3
1071			5.0	482.2

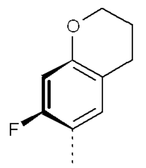
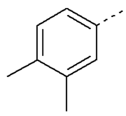
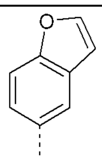
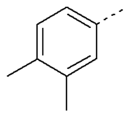
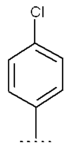
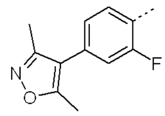
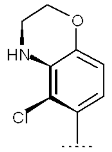
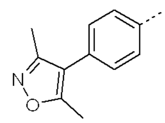
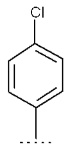
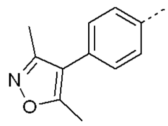
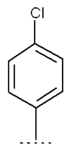
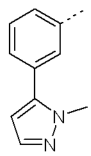
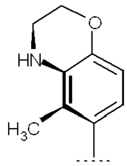
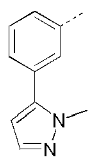
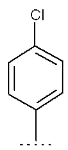
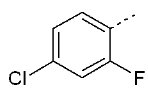
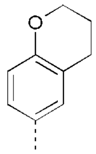
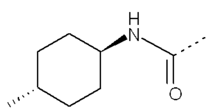
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1072			5.6	532.2
1073			5.7/5.8 *	514.2/ 516.2 518.2
1074			5.3/5.4 *	480.2/ 482.2
1075			5.5/5.6 *	498.2 500.2
1076			5.4/5.5 *	498.2/ 500.2
1077			5.1	544.3
1078			5.3	478.2
1079			5.8	556.2/ 558.2
1080			6.0/6.1 *	494.2

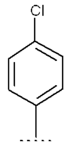
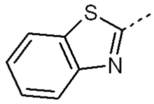
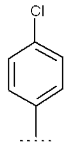
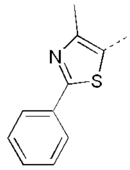
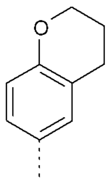
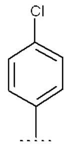
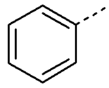
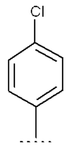
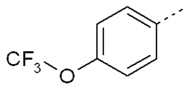
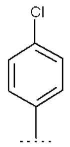
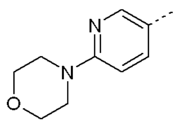
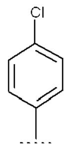
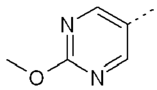
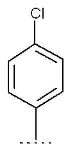
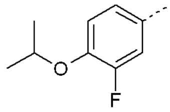
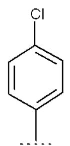
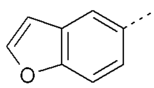
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1081			6.2	498.2/ 500.2
1082			5.6/5.7 *	542.2/ 544.2
1083			5.6	538.2/ 540.2
1084			4.4	555.2
1085			6.1	478.3
1086			6.0	482.2
1087			5.4/5.5 *	559.3
1088			5.1/5.2 *	544.3
1089			5.1/5.2 *	544.3

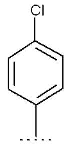
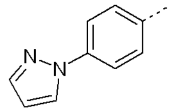
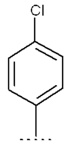
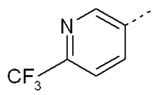
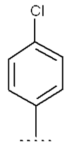
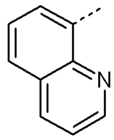
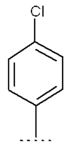
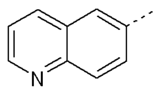
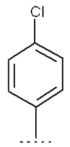
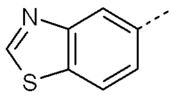
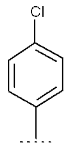
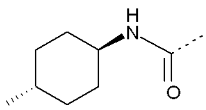
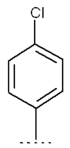
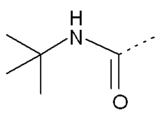
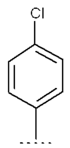
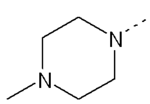
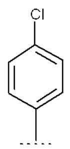
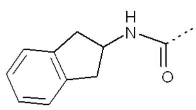
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1090			5.1/5.2 *	575.3
1091			4.3	541.3
1092			4.3	555.3
1093			4.1	523.3
1094			4.2	537.3
1095			5.0/5.1 *	553.3
1096			5.4/5.5 *	554.3
1097			4.7/4.8 *	524.3
1098			5.6	526.3
1099			6.2	478.3

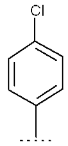
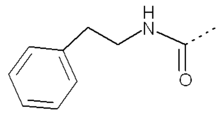
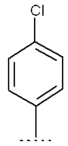
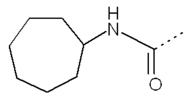
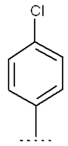
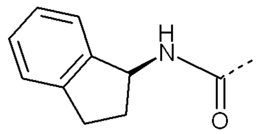
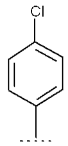
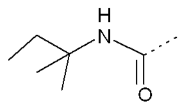
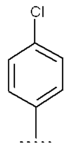
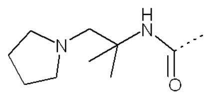
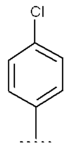
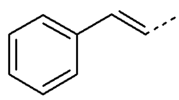
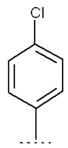
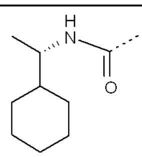
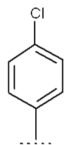
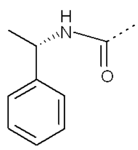
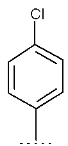
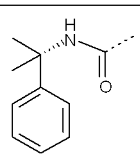
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1100			5.6	557.2
1101			6.0	540.2
1102			5.6	538.3
1103			5.9	540.3
1104			5.1	480.3 482.3
1105			6.0	478.3
1106			5.3	513.3
1107			5.2	475.3
1108			6.1	444.3

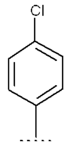
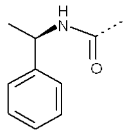
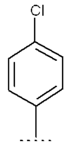
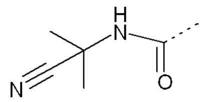
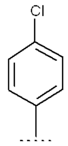
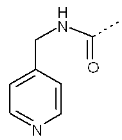
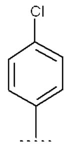
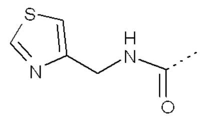
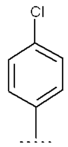
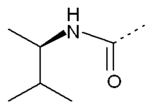
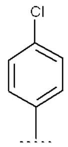
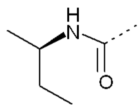
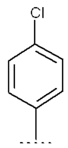
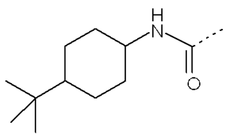
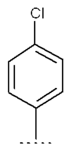
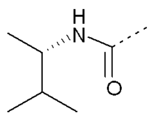
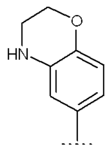
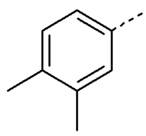
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1109			5.3**	509.3/ 511.3
1110			6.0**	488.4
1111			5.8	452.3/ 454.3
1112			5.7/5.8 *	512.2/ 514.2
1113			6.0**	489.4
1114			6.0	494.4
1115			6.2	555.4
1116			4.7**	511.3
1117			6.5**	508.1 510.1

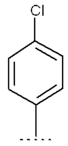
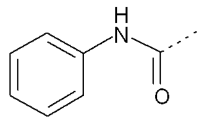
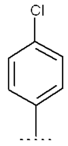
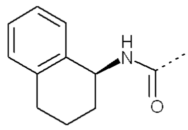
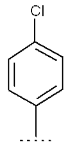
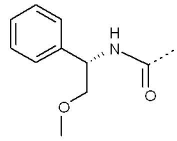
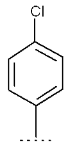
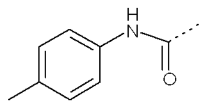
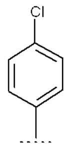
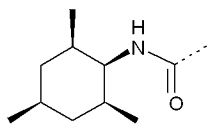
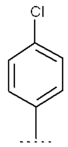
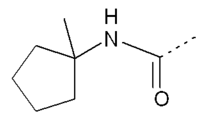
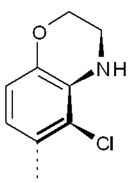
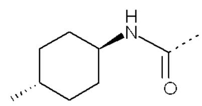
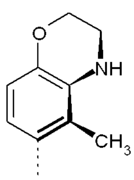
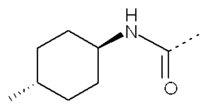
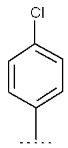
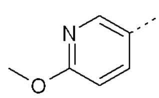
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1118			6.5**	492.4
1119			3.7*	458.4
1120			6.2	537.2/ 539.2
1121			3.5**	576.1/ 578.1
1122			3.7	519.1/ 521.1
1124			5.1	504.2/ 506.2
1125			4.6**	541.3
1126			5.9	476.1/ 478.1/ 480.1
1127			6.2*	509.3

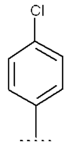
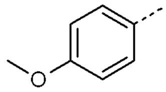
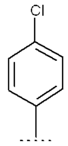
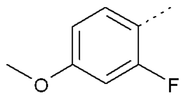
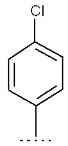
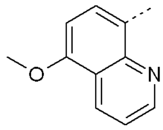
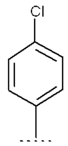
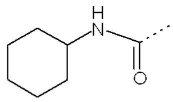
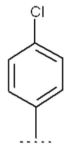
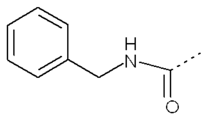
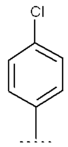
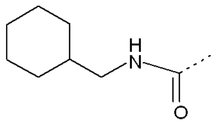
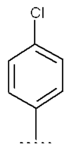
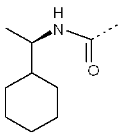
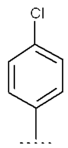
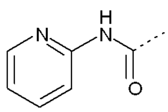
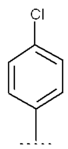
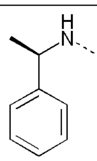
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1128			7.3	481.1/ 483.1
1129			6.2	521.1/ 523.1
1130		$-CH_3$	4.1/4.2 *	384.2
1131			5.0	424.2/ 426.2
1132			5.8	508.1/ 510.1
1133			4.4	510.2/ 512.2
1134			4.8	456.2/ 458.2
1135			5.7	500.2/ 502.2
1136			5.3	464.1/ 466.1

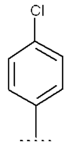
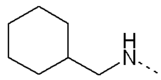
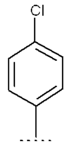
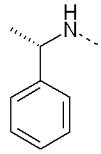
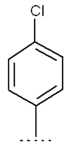
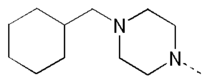
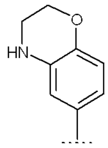
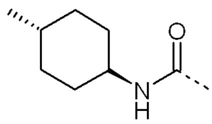
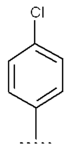
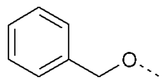
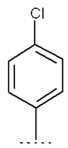
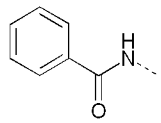
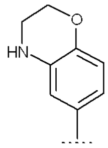
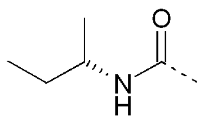
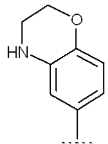
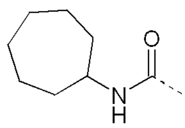
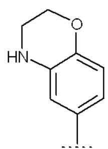
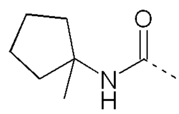
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1137			5.2	490.2/ 492.2
1138			5.9	493.1/ 495.1
1139			4.9	475.1/ 477.2
1140			4.2	475.2/ 477.2
1141			4.9	481.1/ 483.1
1142			6.6	487.2/ 489.2
1143			6.6	447.2/ 449.2
1144			4.1	446.2/ 448.2
1145			6.5	507.1/ 509.1

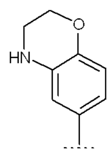
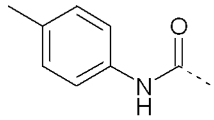
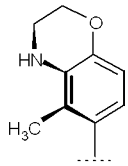
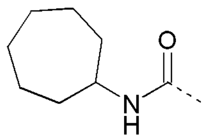
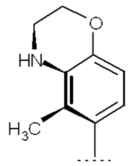
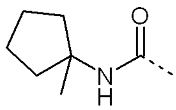
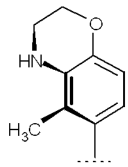
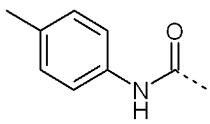
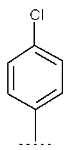
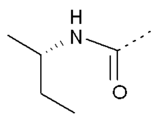
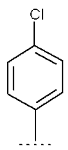
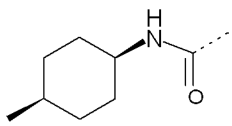
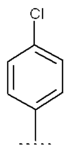
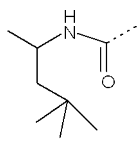
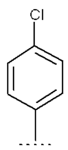
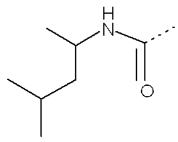
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1146			6.4	495.1/ 497.1
1147			6.5	487.2/ 489.2
1148			6.6	507.1/ 509.1
1149			6.3	461.1/ 463.1
1150			4.8	516.2/ 518.2
1151			5.5	450.1/ 452.1
1152			6.7	501.2/ 503.2
1153			6.5	495.1/ 497.1
1154			6.6	509.2/ 511.2

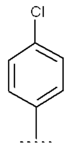
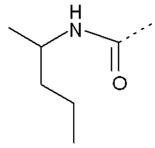
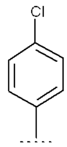
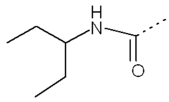
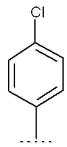
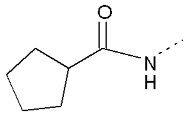
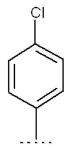
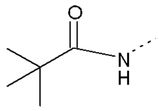
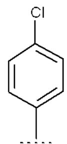
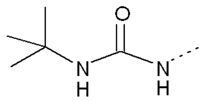
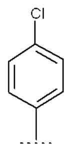
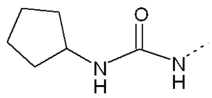
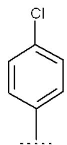
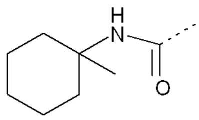
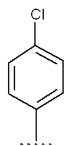
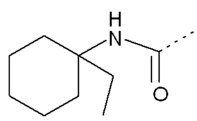
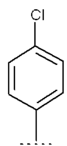
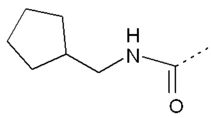
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1155			5.6	495.1/ 497.1
1156			6.1	458.1/ 460.1
1157			4.4	482.2/ 484.2
1158			5.4	488.2/ 490.2
1159			6.3	461.2/ 463.1
1160			6.0	447.1/ 449.1
1161			7.0	529.2/ 531.2
1162			6.2	461.2/ 463.2
1163			4.9/5.5*	475.5

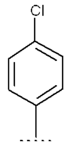
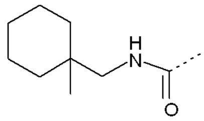
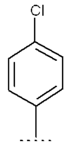
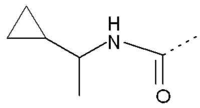
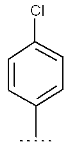
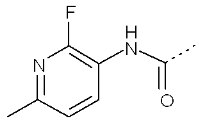
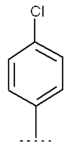
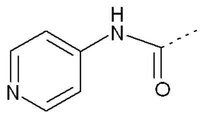
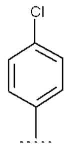
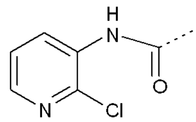
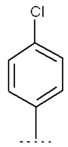
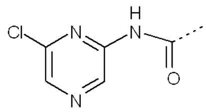
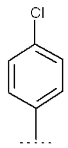
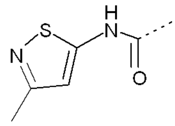
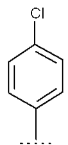
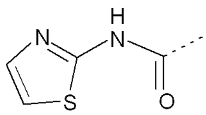
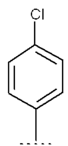
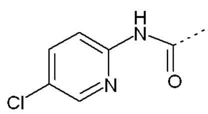
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1164			6.7	467.1/ 469.1
1165			6.7	521.1/ 523.2
1166			6.4	525.1/ 527.1
1167			6.9	481.0/ 483.0
1168			7.1	515.1/ 517.1
1169			6.3	473.1/ 475.1
1170			6.3*	544.3/ 546.3
1171			5.7*	524.2
1172			4.9	455.1/ 457.1

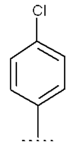
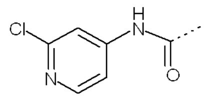
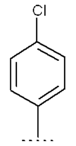
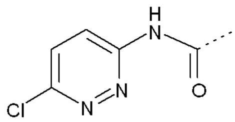
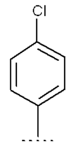
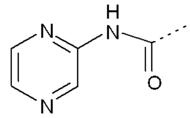
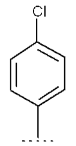
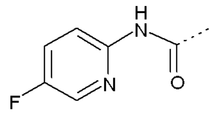
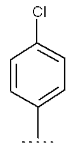
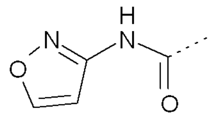
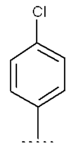
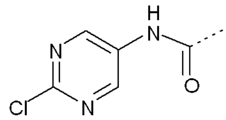
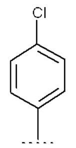
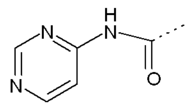
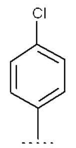
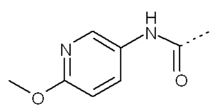
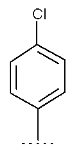
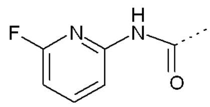
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1173			5.2	454.1/ 456.1
1174			5.3	472.1/ 474.1
1175			5.2	505.1/ 507.1
1176			6.3	473.1/ 475.1
1177			6.4	481.1/ 483.1
1178			6.6	487.1/ 489.1
1179			6.8	501.1/ 503.1
1180			6.6	468.1/ 470.1
1181			5.6	467.3/ 469.3

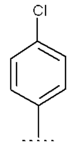
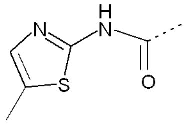
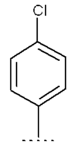
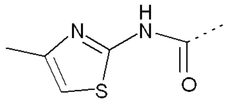
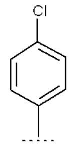
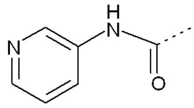
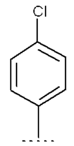
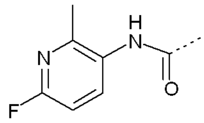
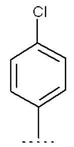
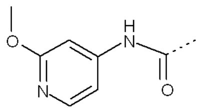
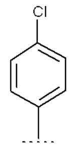
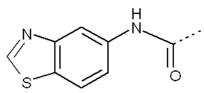
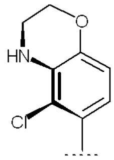
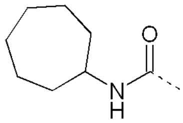
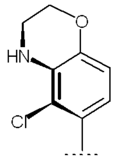
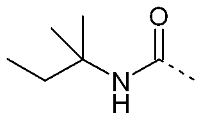
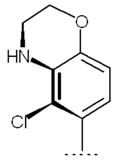
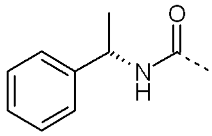
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1182			5.3	459.2/ 461.1
1183			5.2	467.1/ 469.1
1184			5.1	528.3/ 530.2
1185			5.2/5.6*	510.3
1186			7.2	454.1/ 456.1
1187			5.3	467.1/ 469.1
1188			4.3/4.7*	470.3
1189			5.1/5.5*	510.3
1190			4.7/5.1*	496.3

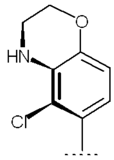
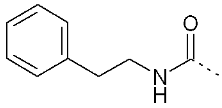
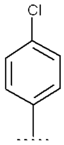
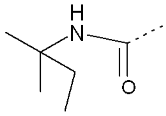
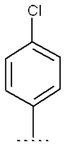
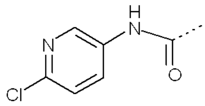
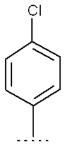
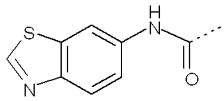
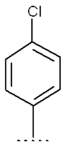
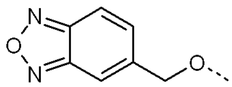
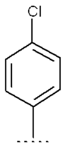
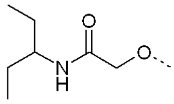
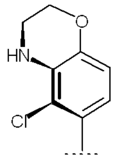
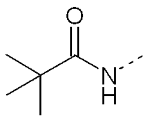
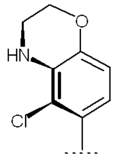
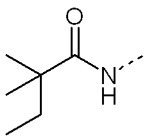
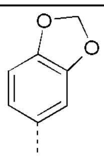
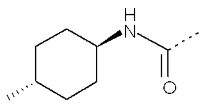
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1191			5.6/6.2*	504.3
1192			5.6**	524.2
1193			5.2**	510.2
1194			6.2**	518.2
1195			5.3	447.1/ 449.1
1196			6.6	487.1/ 489.1
1197			9.0	489.2/ 491.2
1198			8.3	475.2/ 477.2

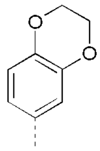
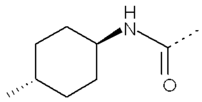
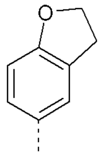
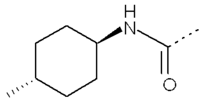
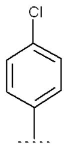
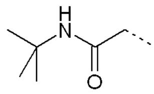
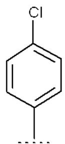
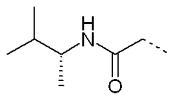
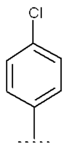
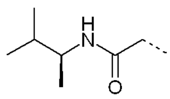
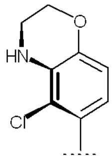
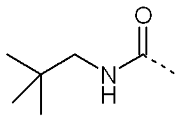
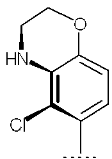
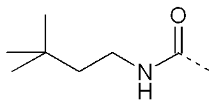
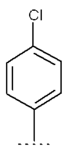
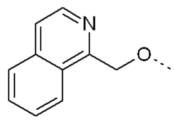
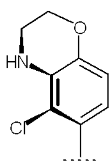
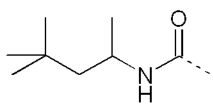
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1199			7.7	461.1/ 463.1
1200			7.6	461.1/ 463.1
1201			5.1	459.1/ 461.1
1202			5.1	447.1/ 449.1
1203			5.2	462.1/ 464.1
1205			5.3	474.1/ 476.1
1206			8.5	487.1/ 489.1
1207			9.4	501.1/ 503.1
1208			8.1	473.1/ 475.1

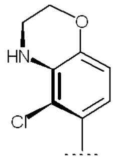
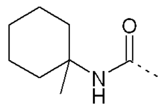
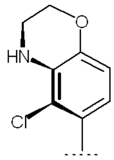
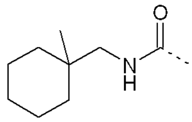
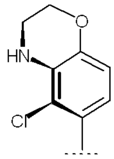
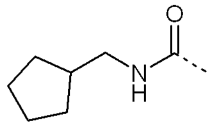
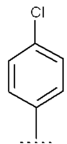
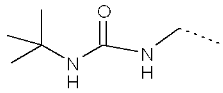
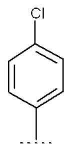
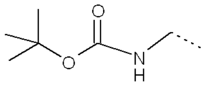
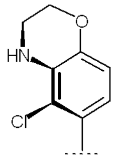
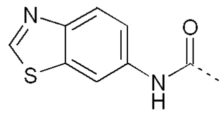
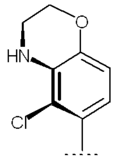
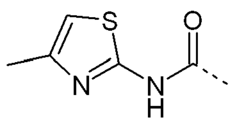
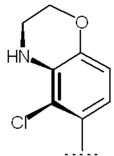
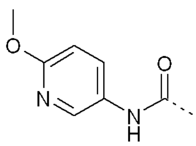
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1209			9.2	501.2/ 503.1
1210			7.1	459.1/ 461.1
1211			4.6	500.1/ 502.1
1212			3.5	468.1/ 470.1
1213			4.6	502.0/ 504.0/ 506.0
1214			4.7	503.0/ 505.0/ 507.0
1215			4.3	488.0/ 490.0
1216			4.4	474.0/ 476.0
1217			4.7	502.0/ 504.0/ 506.0

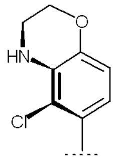
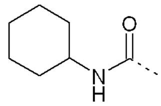
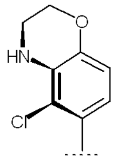
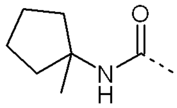
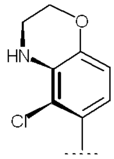
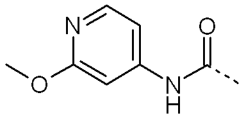
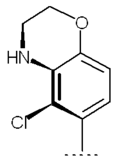
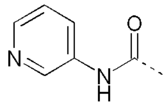
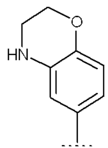
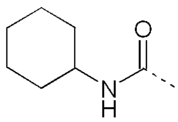
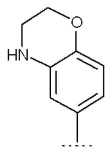
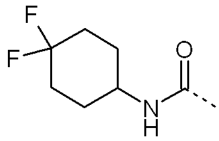
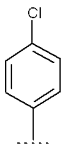
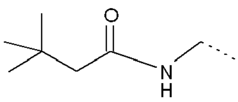
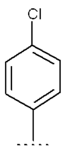
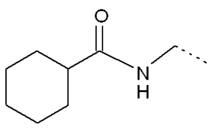
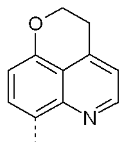
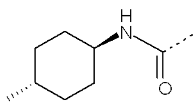
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1218			4.5	502.0/ 504.0/ 506.0
1219			4.5	503.0/ 505.0/ 507.0
1220			4.4	469.1/ 471.1
1221			4.6	486.1/ 488.1
1222			4.4	458.1/ 460.1
1223			4.5	503.0/ 505.0/ 507.0
1224			4.2	469.1/ 471.1
1225			4.3	498.1/ 500.1
1226			4.6	486.0/ 488.0

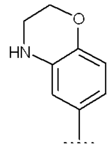
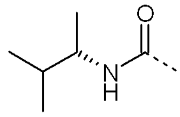
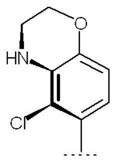
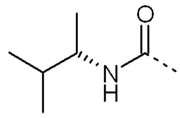
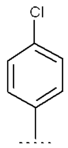
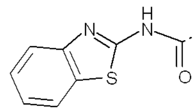
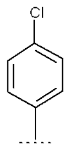
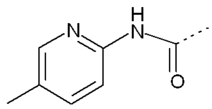
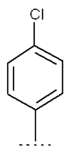
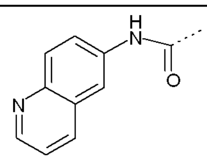
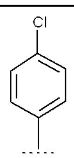
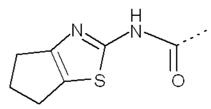
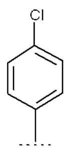
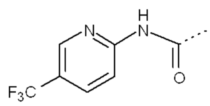
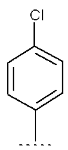
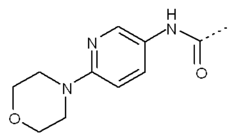
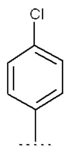
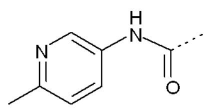
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1227			4.4	488.0/ 490.0
1228			4.4	488.0/ 490.0
1229			3.4	468.1/ 470.1
1230			4.5	500.1/ 502.1
1231			3.9	498.1/ 500.1
1232			4.4	524.0/ 526.0
1233			6.2**	544.1/ 546.1
1234			5.8**	518.1/ 520.1
1235			6.1**	552.1/ 554.1

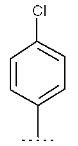
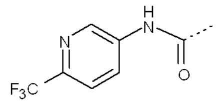
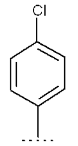
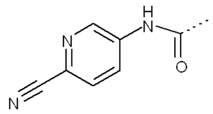
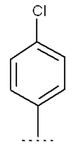
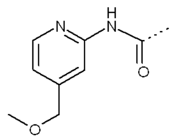
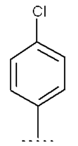
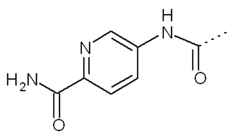
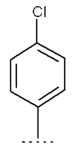
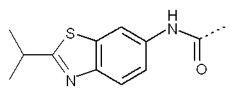
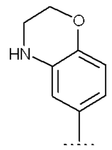
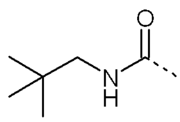
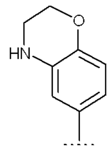
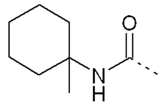
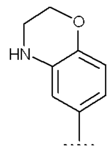
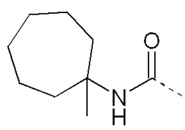
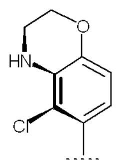
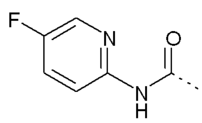
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1236			6.0**	552.1/ 554.1
1237			5.4	461.1/ 463.1
1238			4.5	502.0/ 504.0/ 506.0
1239			4.4	524.0/ 526.0
1240			7.2	496.0/ 498.0
1241			6.7	491.1/ 493.1
1242			4.7**	504.1/ 506.1
1243			4.9**	518.1/ 520.1
1244			4.2*	497.2

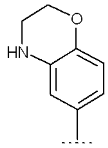
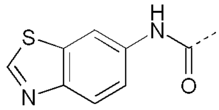
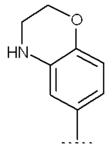
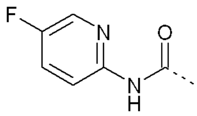
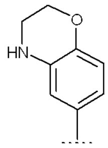
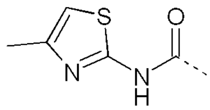
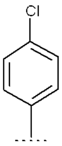
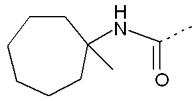
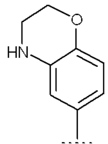
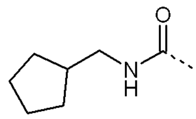
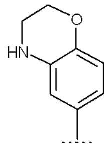
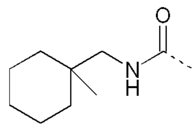
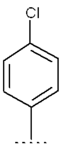
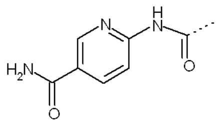
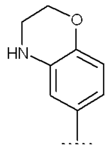
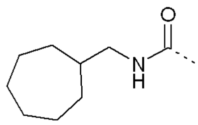
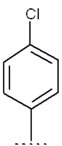
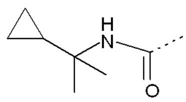
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1245			4.2*	511.2
1246			4.2*	495.1
1247			4.9	461.1/ 463.1
1248			5.1	475.1/ 477.1
1249			5.1	475.1/ 447.1
1250			7.0**	518.2/ 520.2
1251			7.6**	532.1/ 534.1
1252			5.3	505.1/ 507.1
1253			8.2**	546.1/ 548.1

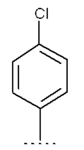
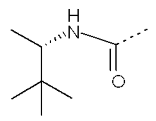
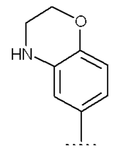
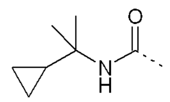
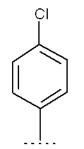
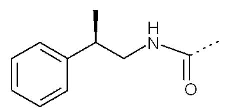
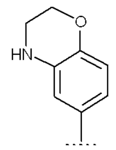
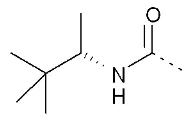
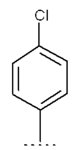
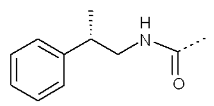
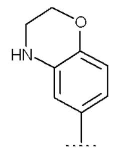
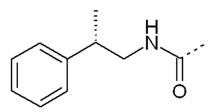
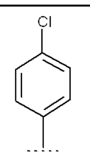
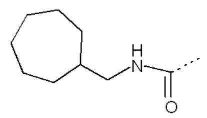
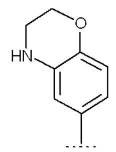
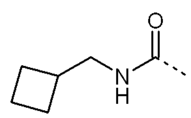
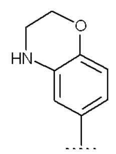
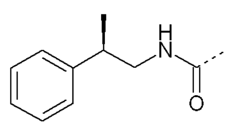
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1254			7.6**	544.1/ 546.1
1255			8.5**	558.1/ 560.1
1256			7.1**	530.1/ 532.1
1257			4.7	476.1/ 478.1
1258			4.9	477.2/ 479.2
1259			6.3**	581.1/ 583.0
1260			6.3**	545.1/ 547.1
1261			6.0**	555.1/ 557.1

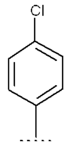
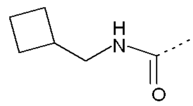
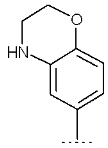
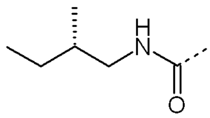
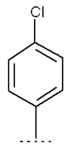
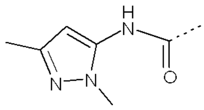
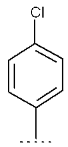
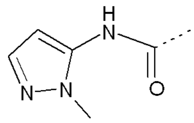
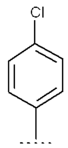
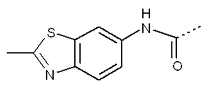
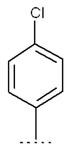
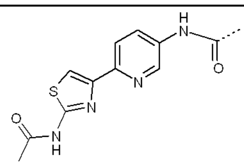
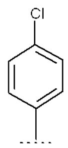
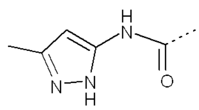
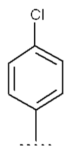
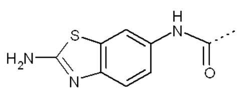
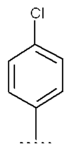
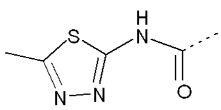
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1262			5.8**	530.2/ 532.2
1263			5.7**	530.2/ 532.2
1264			5.1**	555.1/ 557.1
1265			4.4**	525.1/ 527.2
1266			4.7/5.2*	496.3
1267			5.3/5.8*	532.3
1268			4.8	475.2/ 477.2
1269			4.9	487.2/ 489.2
1270			5.3**	546.2

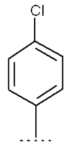
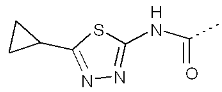
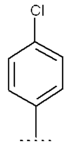
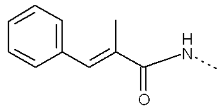
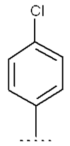
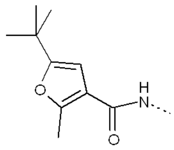
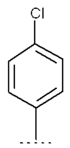
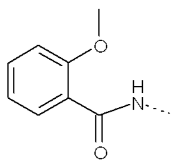
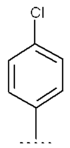
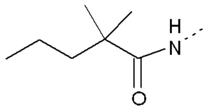
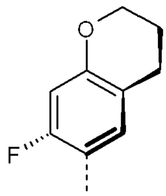
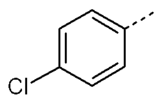
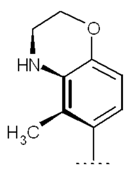
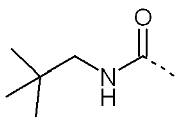
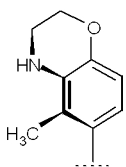
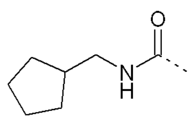
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1271			4.6/5.1*	484.3
1272			5.7**	518.2/ 520.2
1273			7.1	524.1/ 526.1
1274			5.8	482.2/ 484.2
1275			5.1	518.2/ 520.2
1276			6.9	514.1/ 516.1
1277			7.2	536.1/ 538.1
1278			4.9	553.2/ 555.2
1279			4.8	482.2/ 484.2

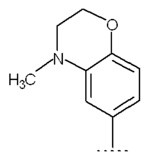
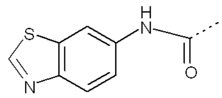
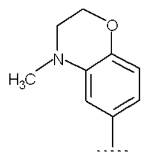
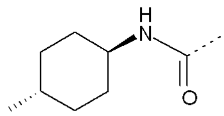
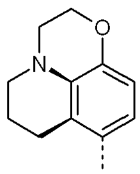
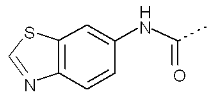
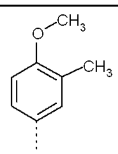
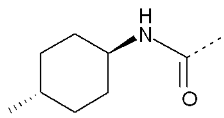
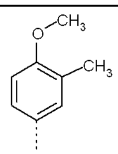
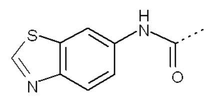
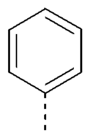
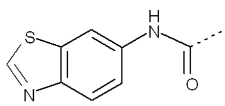
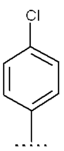
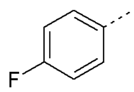
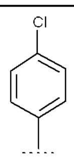
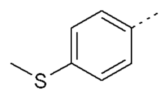
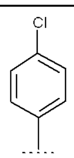
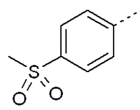
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1280			6.9	536.1/ 538.1
1281			6.7	493.1/ 495.1
1282			5.8	512.2/ 514.2
1283			5.9	511.2/ 513.2
1284			7.1	566.2/ 568.2
1285			5.8/6.4*	484.3
1286			6.2/6.8*	510.3
1287			6.5/7.3*	524.3
1288			4.4**	543.2/ 545.2

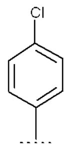
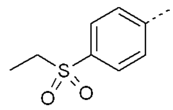
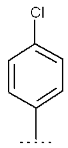
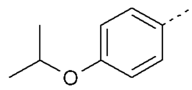
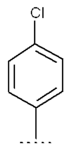
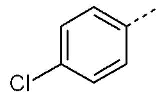
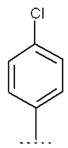
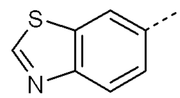
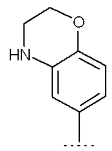
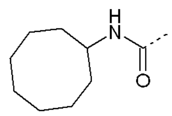
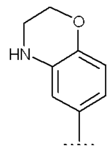
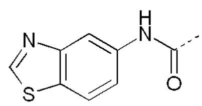
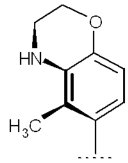
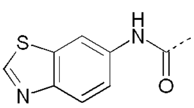
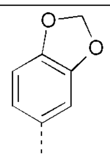
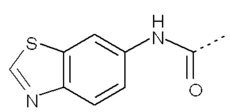
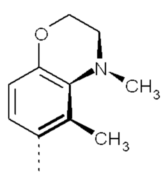
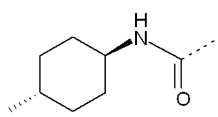
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1289			3.8/4.1*	547.2
1290			4.0/4.3*	509.2
1291			3.8/4.1*	511.2
1292			9.3	501.1/ 503.1
1293			5.9/6.5*	496.2
1294			6.8/7.7*	524.2
1295			5.9	511.2/ 513.2
1296			5.6/6.0*	524.2
1297			6.2	473.1/ 475.1

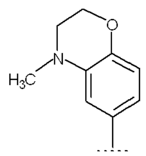
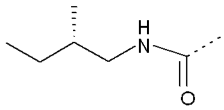
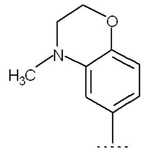
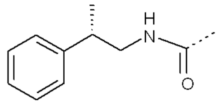
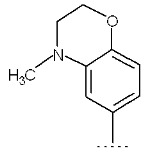
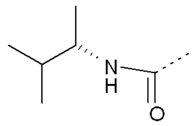
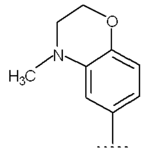
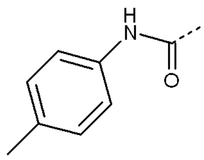
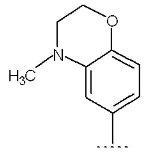
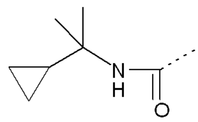
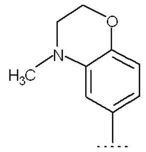
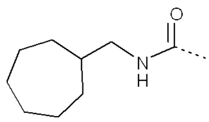
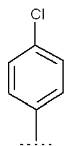
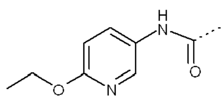
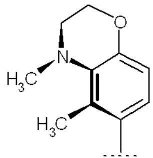
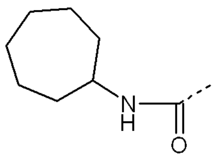
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1298			6.5	475.3/ 477.2
1299			4.7/5.1*	496.3
1300			6.5	509.0/ 511.0
1301			4.9/5.4*	498.1
1302			6.5	509.0 511.0
1303			5.1/5.6*	532.3
1304			6.8	501.1/ 503.1
1305			4.5/5.0*	482.3
1306			5.1/5.5*	532.3

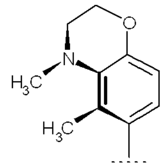
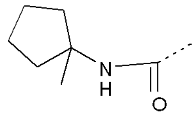
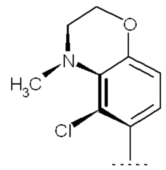
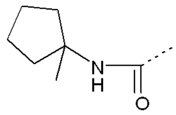
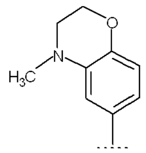
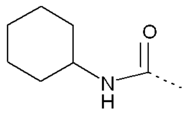
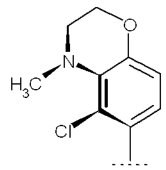
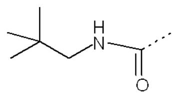
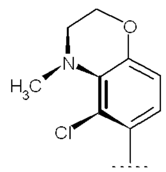
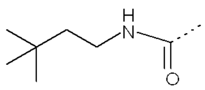
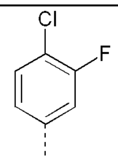
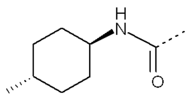
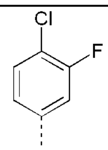
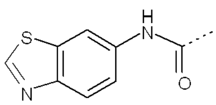
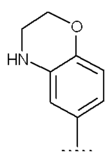
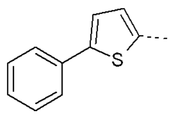
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1307			6.2	459.1/ 461.0
1308			4.8/5.2*	484.3
1309			6.0	485.2/ 487.2
1310			6.0	471.2/ 473.2
1311			6.7	538.1/ 540.2
1312			5.4	608.2/ 610.2
1313			5.6	471.1/ 473.1
1314			5.0	539.1/ 541.1
1315			6.4	489.0/ 491.0

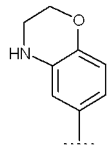
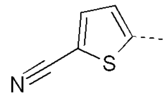
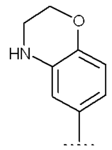
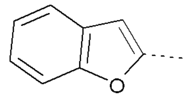
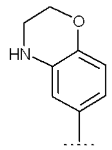
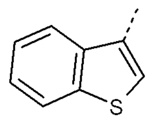
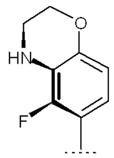
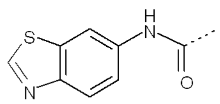
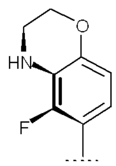
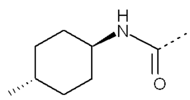
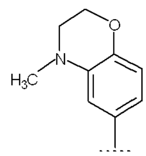
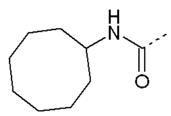
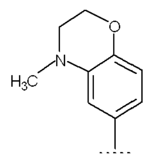
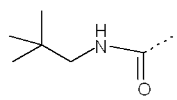
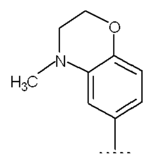
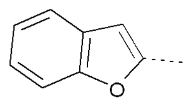
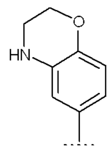
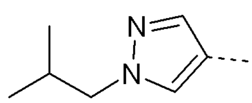
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1316			6.7	515.0/ 517.0
1317			6.2	507.0/ 509.0
1318			6.2	527.1/ 529.1
1319			5.3	497.0/ 499.0
1320			6.1	475.1/ 477.1
1321			5.6**	498.1 500.1
1322			6.1**	498.3
1323			6.2**	510.3

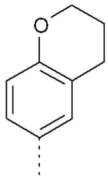
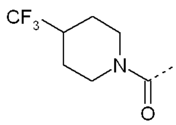
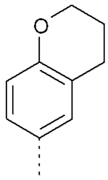
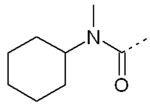
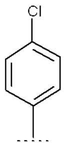
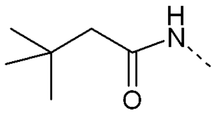
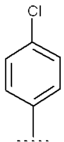
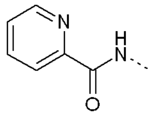
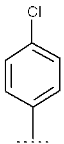
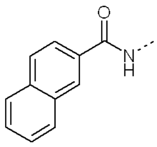
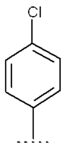
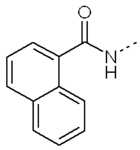
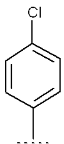
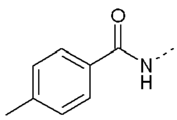
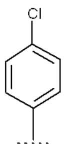
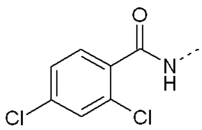
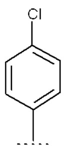
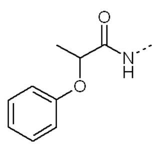
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1324			4.2/4.3*	561.2
1325			4.1/4.2*	524.3
1326			7.9**	587.3
1327			7.5/7.8*	497.2
1328			7.8/8.2*	534.1
1329			7.5	490.1
1330			5.2	442.1/ 444.1
1331			5.5	470.2/ 472.1
1332			4.9	502.2/ 504.1

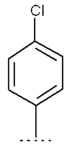
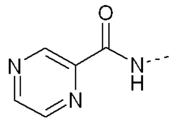
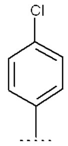
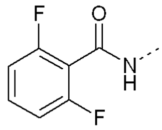
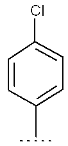
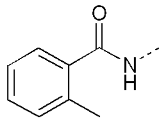
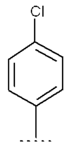
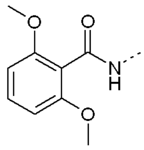
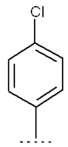
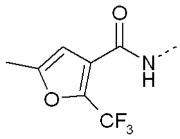
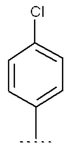
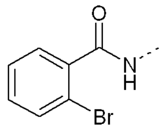
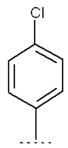
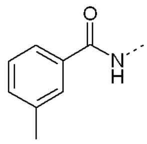
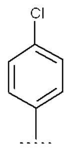
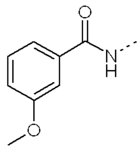
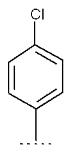
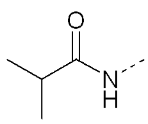
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1333			5.1	516.2/ 518.1
1335			5.7	482.2/ 484.2
1336			5.5	458.1/ 460.1/ 462.1
1337			4.9	481.1/ 483.1
1338			6.1/6.7*	524.3
1339			3.7/4.0*	547.2
1340			4.1**	561.2
1341			4.2	534.2
1342			5.7**	538.2

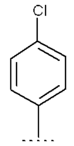
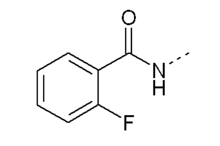
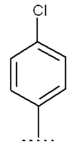
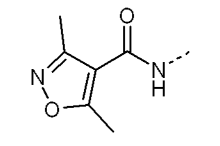
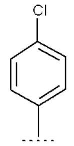
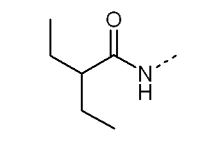
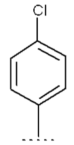
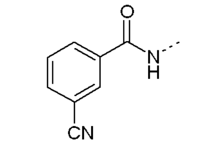
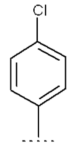
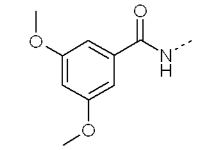
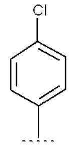
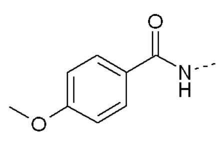
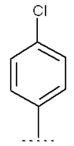
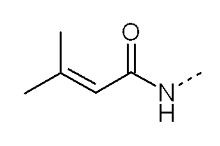
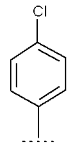
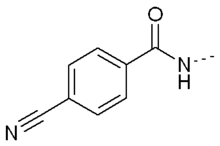
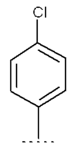
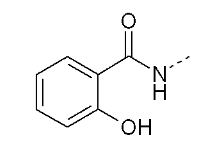
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1343			5.5/5.7*	498.1
1344			5.8/6.0*	546.1
1345			5.3/5.5*	498.1
1346			6.4/6.5*	518.1
1347			5.4/5.5*	510.1
1348			6.2/6.4*	538.2
1349			6.6	512.2/ 514.2
1350			5.6**	538.3

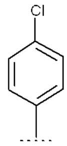
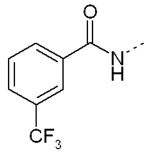
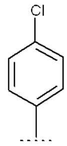
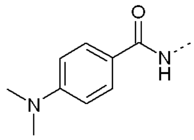
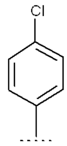
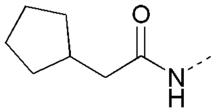
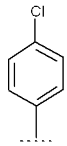
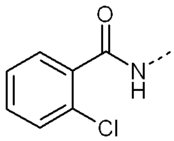
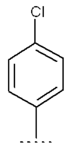
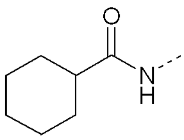
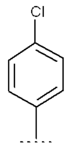
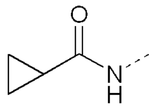
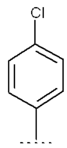
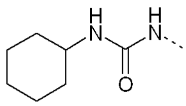
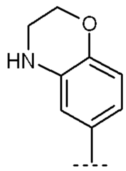
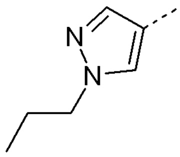
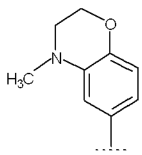
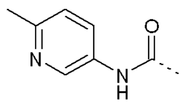
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1351			5.2**	524.3
1352			5.8**	544.3/ 546.3
1353			5.4/5.6*	510.3
1354			7.1**	532.2/ 534.2
1355			7.8**	546.2/ 548.2
1356			8.9	505.1/ 507.1
1357			8.6	542.0/ 544.0
1358			5.4/5.9*	529.2

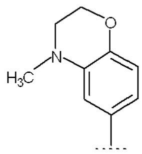
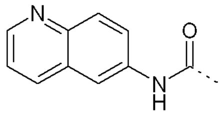
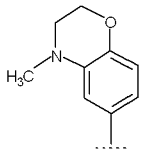
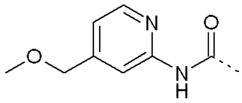
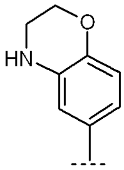
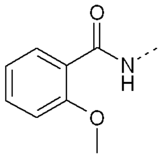
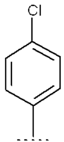
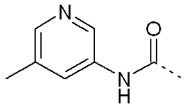
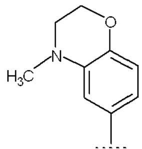
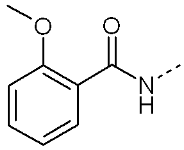
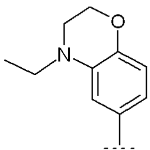
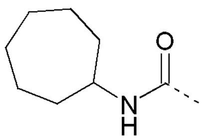
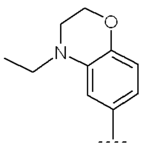
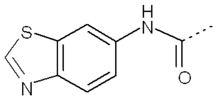
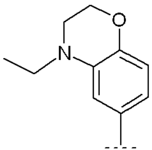
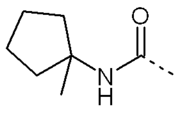
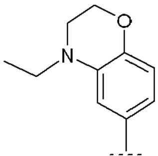
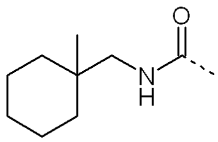
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1359			5.2/5.8*	478.2
1360			4.7/5.2*	487.2
1361			4.7/5.1*	503.2
1362			7.1**	565.2
1363			7.3**	528.3
1364			7.1/7.4*	538.3
1365			6.3/6.6*	498.3
1366			5.3/5.5*	501.2
1367			4.3/4.7*	493.3

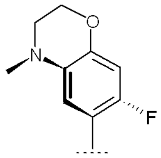
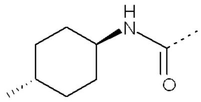
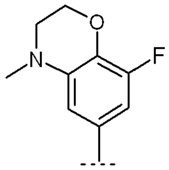
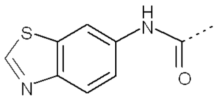
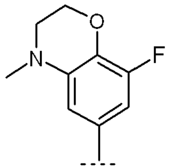
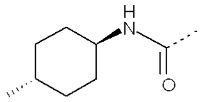
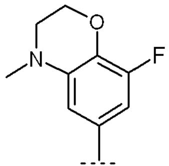
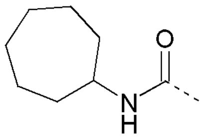
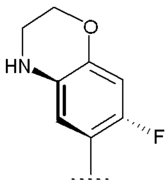
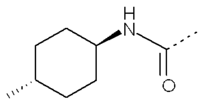
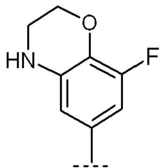
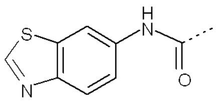
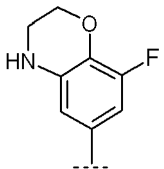
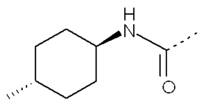
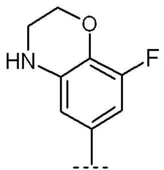
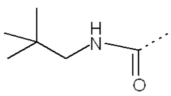
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1368			5.6	549.3
1369			4.6	509.3
1370			1.9$	461.2/ 463.2
1371			1.9$	468.1/ 470.1
1372			2.1$	517.2/ 519.2
1373			2.1$	517.2/ 519.2
1374			2.0$	481.2/ 483.1
1375			2.2$	537.0/ 539.0
1376			2.1$	511.2/ 513.1

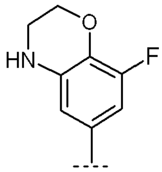
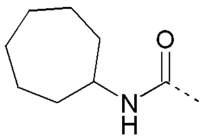
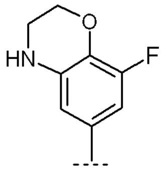
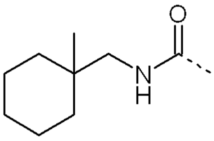
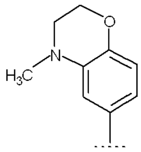
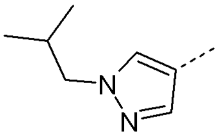
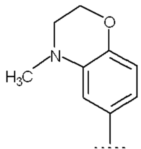
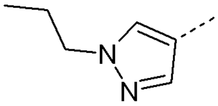
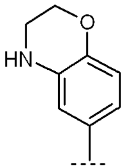
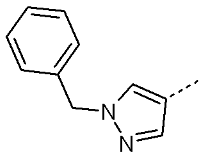
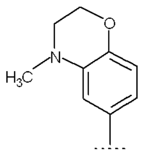
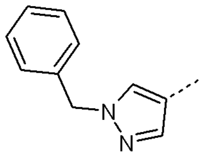
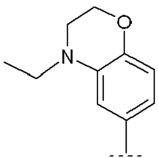
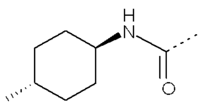
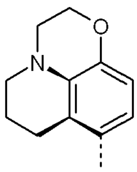
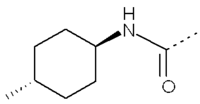
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1377			1.8$^{\$}$	469.1/ 471.1
1378			2.0$^{\$}$	503.1/ 505.1
1379			2.0$^{\$}$	481.1/ 483.1
1380			1.9$^{\$}$	527.1/ 529.1
1381			2.1$^{\$}$	539.1/ 541.1
1382			2.0$^{\$}$	546.0/ 548.0
1383			2.0$^{\$}$	481.2/ 483.1
1384			2.0$^{\$}$	497.1/ 499.1
1385			1.7$^{\$}$	433.2/ 435.1

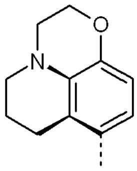
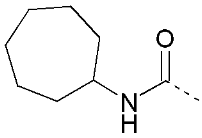
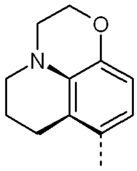
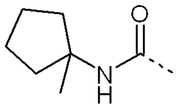
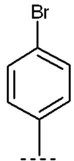
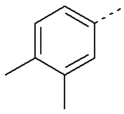
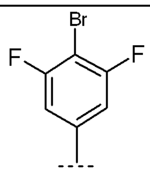
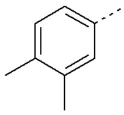
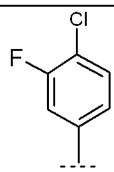
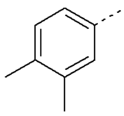
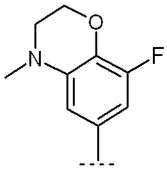
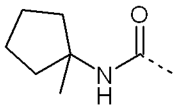
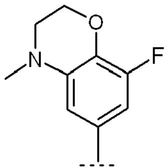
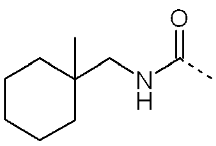
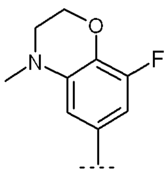
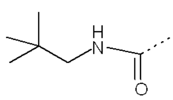
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1386			2.0$	485.1/ 487.1
1387			1.9$	486.1/ 488.1
1388			1.9$	461.2/ 463.2
1389			2.0$	492.1/ 494.1
1390			2.0$	527.1/ 529.1
1391			1.9$	497.1/ 499.1
1392			1.8$	445.2/ 447.2
1393			2.0$	492.1/ 494.1
1394			1.9$	483.1/ 485.1

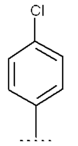
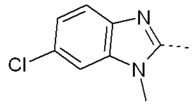
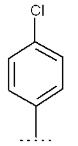
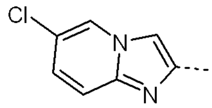
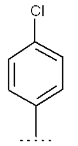
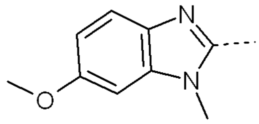
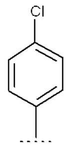
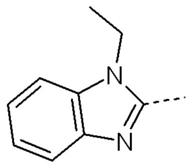
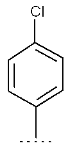
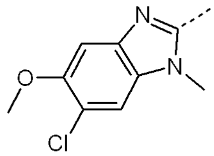
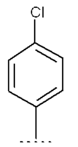
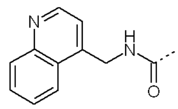
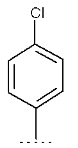
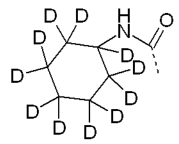
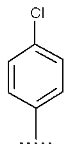
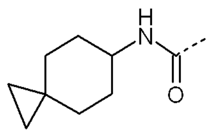
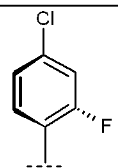
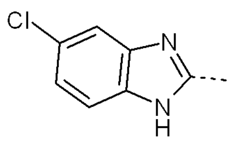
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1395			2.1$	535.1/ 537.1
1396			2.0$	510.2/ 512.1
1397			2.0$	473.2/ 475.2
1398			2.0$	501.1/ 503.1
1399			2.0$	473.2/ 475.2
1400			1.7$	431.2/ 433.1
1401			2.0$	488.2/ 490.2
1402			4.0/4.4*	479.1
1403			4.4/4.5*	519.2

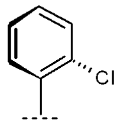
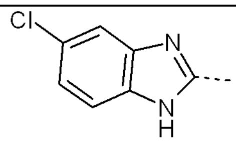
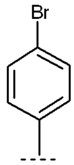
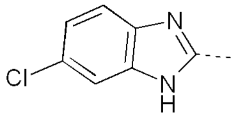
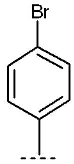
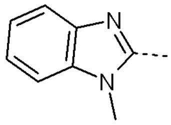
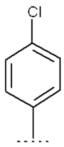
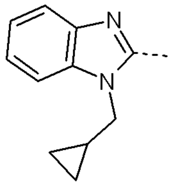
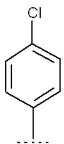
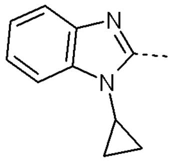
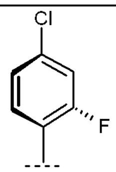
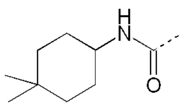
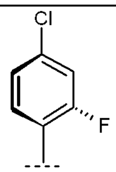
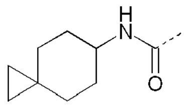
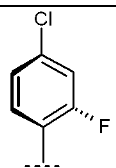
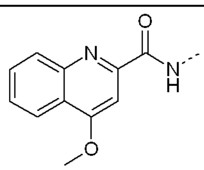
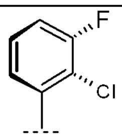
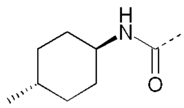
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1404			4.7/4.8*	555.2
1405			5.2/5.4*	549.3
1406			4.5/4.8*	520.2
1407			4.9	482.2/ 484.2
1408			4.9/5.1*	534.3
1409			6.1/6.2*	538.4
1410			6.3/6.4*	575.3
1411			5.7/5.8*	524.4
1412			6.6	552.4

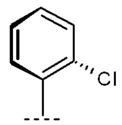
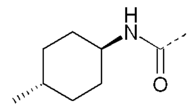
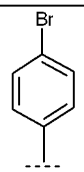
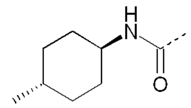
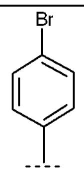
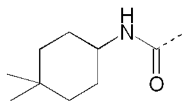
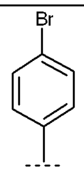
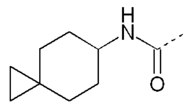
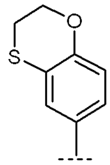
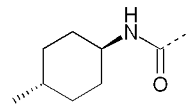
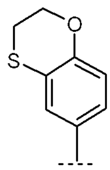
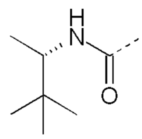
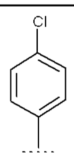
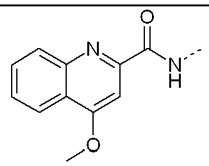
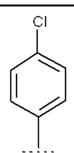
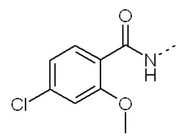
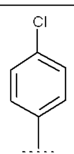
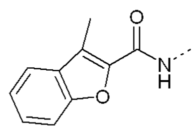
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1413			6.5**	542.4
1414			6.3/6.4*	579.3
1415			6.3/6.4*	542.2
1416			6.2/6.3*	542.2
1417			6.2**	528.3
1418			4.0/4.2*	565.1
1419			4.0/4.2*	528.2
1420			3.8/4.0*	502.3

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1421			3.9/4.1*	528.3
1422			4.2/4.3*	542.3
1423			4.8/5.0*	507.3
1424			4.6/4.7*	493.3
1425			4.5/4.8*	527.3
1426			5.0/5.1*	541.3
1427			6.3	538.4
1428			2.2$	550.4

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1429			2.2$	550.2
1430			2.1$	536.2
1431			5.5	496.1/ 498.1
1432			6.6	532.0/ 534.0
1433			6.0	470.1/ 472.1
1434			5.8/5.9*	528.2
1435			6.6	556.3
1436			6.0/6.1	516.2

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1437			2.0$	512.2/ 514.2/ 516.2
1438			4.9	498.1/ 500.1
1439			2.1$	508.0/ 510.0
1440			2.8$	492.1/ 494.1
1441			1.5$	542.2/ 544.2/ 546.2
1442			4.8	532.2/ 534.2
1443			6.4	484.3/ 486.3
1444			4.4	499.2/ 500.2
1445			4.2**	516.0/ 518.0/ 520.0

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1446			4.1**	498.0/ 500.0/ 502.0
1447			4.2	542.0/ 544.0/ 546.0
1448			3.5	522.1/ 524.1
1449			2.2$	518.2/ 520.2
1450			2.1$	504.0/ 506.0
1451			7.0**	519.2/ 521.2
1452			4.6**	517.3/ 519.3
1453			6.6**	566.2/ 568.2
1454			2.9**$	505.2/ 507.2

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1455			6.7**	487.4/ 489.4
1456			5.4	531.2/ 533.2
1457			7.6	545.2/ 547.2
1458			7.4	543.2/ 545.2
1459			6.8	527.3
1460			6.6	512.2
1461			6.7	548.3/ 550.2
1462			2.0$	531.2/ 533.1/ 535.1
1463			2.2$	521.3/ 523.3

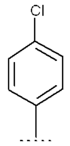
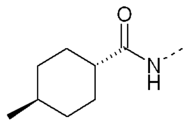
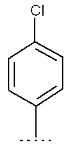
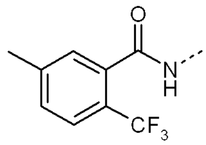
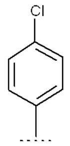
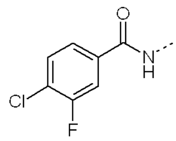
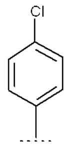
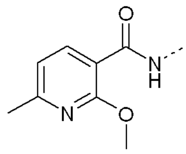
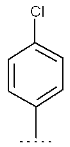
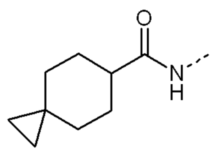
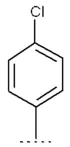
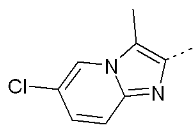
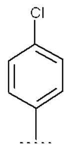
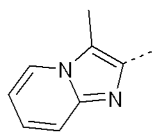
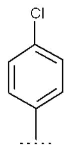
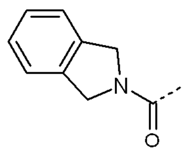
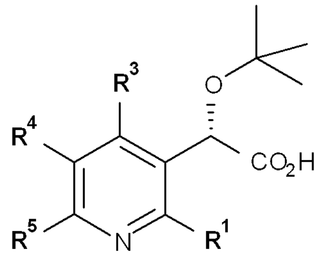
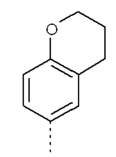
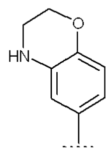
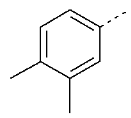
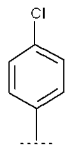
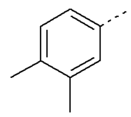
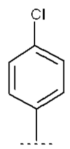
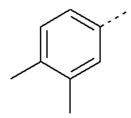
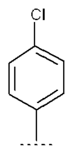
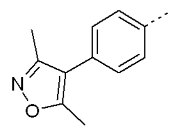
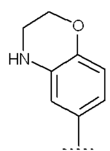
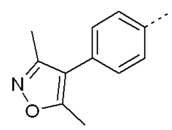
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1464			2.0$	487.3/ 489.3
1465			2.7$	549.0/ 551.0
1466			2.2$	519.1/ 521.1/ 523.1
1467			5.5	512.2/ 514.2
1468			4.0	499.3/ 501.3
1469			4.8	511.9/ 513.9
1470			4.5	487.0/ 480.0
1471			6.3	493.1/ 495.1

TABLE 2



*presence of 2 inter-converting conformers by HPLC

**Most active atropisomer

Cpd	R^1	R^3	R^4	R^5	t_R (min)	MS $(M+H)^+$
2001	$-CH_3$		-CN	$-CH_3$	5.9	395.1
2002	$-CH_2SMe$		$-CH_3$		5.1/5.6 *	521.2
2003	$-CH_2OMe$		$-CH_3$		5.7	482.0/ 484.0
2004	$-CH_2OEt$		$-CH_3$		5.8	496.2/ 498.2
2005	$-CH_3$		-CN		8.5	530.2/ 532.2
2006	$-CH_3$		-CN		7.2*	553.2

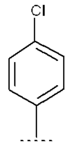
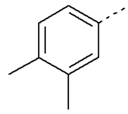
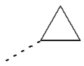
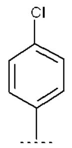
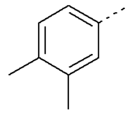
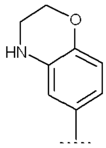
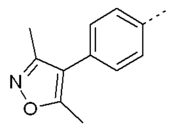
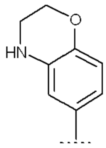
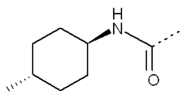
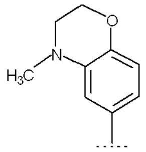
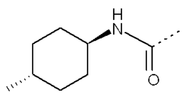
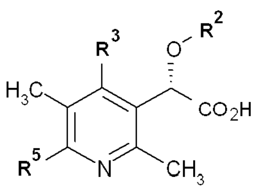
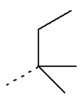
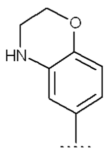
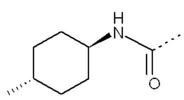
Cpd	R^1	R^3	R^4	R^5	t_R (min)	MS $(M+H)^+$
2007	$-CH=CH_2$		$-CH_3$		5.6	464.2/ 466.2
2008			$-CH_3$		5.8	478.2/ 480.2
2009	$-CH_3$		-F		6.2	546.1
2010	$-CH_2OMe$		$-CH_3$		4.4/5.0 *	540.4
2011	$-CH_2OMe$		$-CH_3$		5.3/5.5 *	554.4

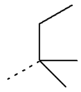
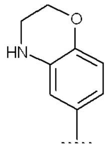
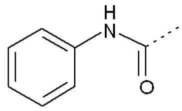
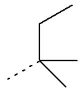
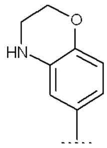
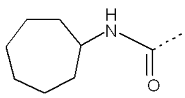
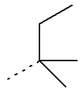
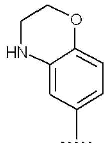
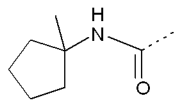
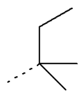
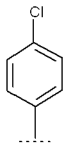
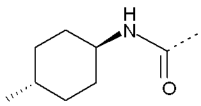
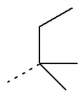
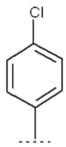
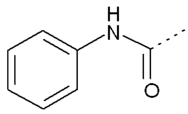
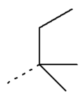
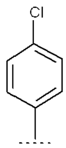
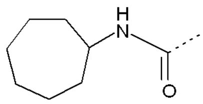
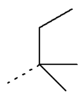
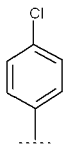
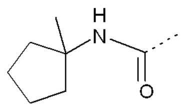
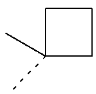
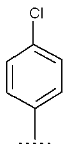
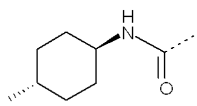
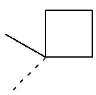
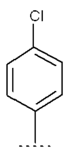
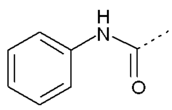
TABLE 3



*presence of 2 inter-converting conformers by HPLC

**Most active atropisomer

Cpd	R^2	R^3	R^5	t_R (min)	MS $(M+H)^+$
3001				5.7/6.2*	524.3

Cpd	R^2	R^3	R^5	t_R (min)	MS $(M+H)^+$
3002				5.9/6.4*	504.3
3003				5.6/6.1*	524.3
3004				5.1/6.6*	510.2
3005				6.8	501.1/ 503.1
3006				6.9	481.1/ 483.1
3007				6.8	501.1/ 503.1
3008				6.6	487.1/ 489.1
3009				6.8	499.1/ 501.1
3010				6.8	479.1/ 481.1

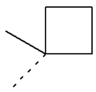
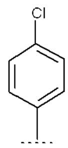
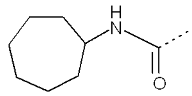
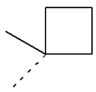
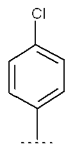
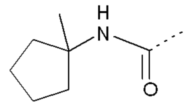
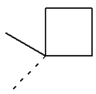
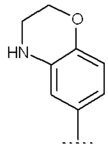
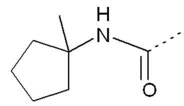
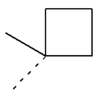
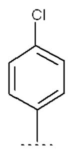
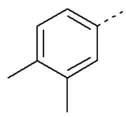
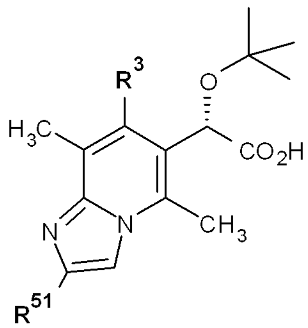
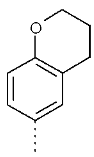
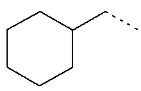
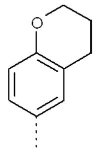
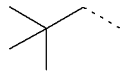
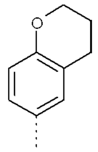
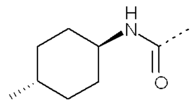
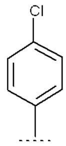
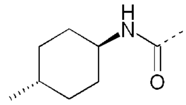
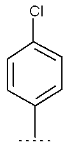
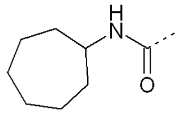
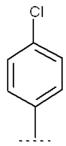
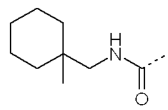
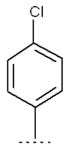
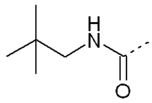
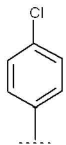
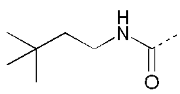
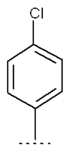
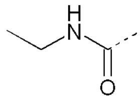
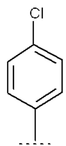
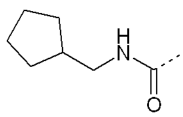
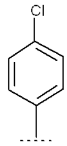
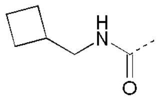
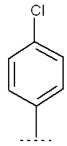
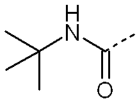
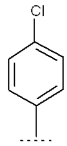
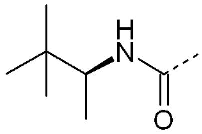
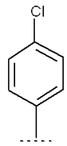
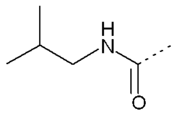
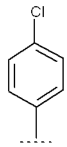
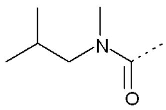
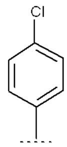
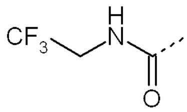
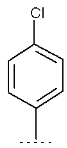
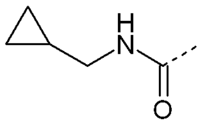
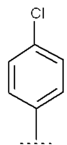
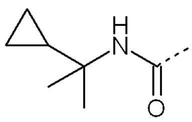
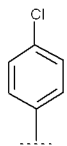
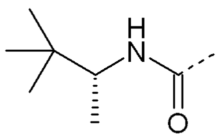
Cpd	R^2	R^3	R^5	t_R (min)	MS $(M+H)^+$
3011				6.7	499.1/ 501.1
3012				6.5	485.1/ 487.1
3013				4.9/5.0*	508.2
3014				5.5	464.2 466.2

TABLE 4



Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
4001			6.3	505.2

Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
4002			5.4	479.2
4003			6.3	548.2
4004			7.1	526.1/ 528.1
4005			6.9	526.1/ 528.1
4006			7.9	540.1/ 542.1
4007			6.6	500.1/ 502.1
4008			7.0	514.1/ 516.1
4009			5.3	458.1/ 460.1
4010			6.7	512.1/ 514.1

Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
4011			6.3	498.1/ 500.1
4012			6.1	486.1/ 488.1
4013			7.0	514.2/ 516.2
4014			6.1	486.1/ 488.1
4015			5.5	500.1/ 502.1
4016			4.7	512.2/ 514.2
4017			4.5	484.3/ 486.3
4018			5.0	512.3/ 514.3
4019			5.1	514.2/ 516.2

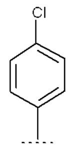
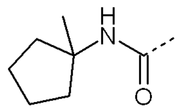
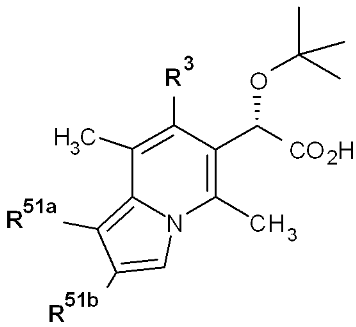
Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
4020			5.0	512.2/ 514.2

TABLE 5



*presence of 2 inter-converting conformers by HPLC

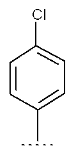
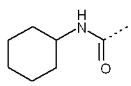
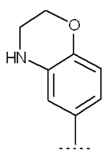
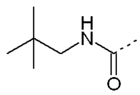
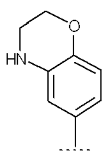
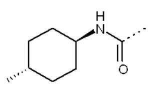
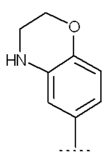
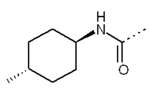
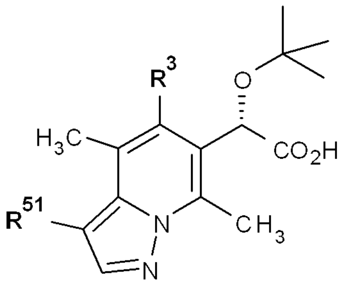
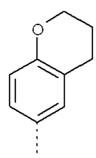
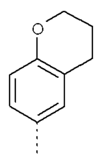
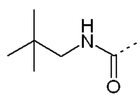
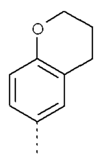
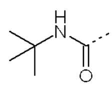
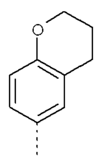
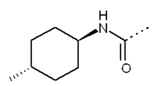
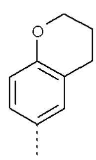
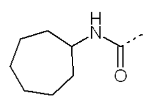
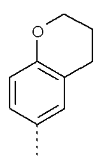
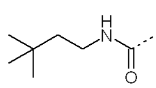
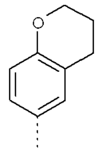
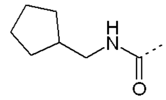
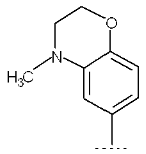
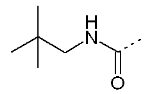
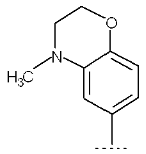
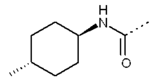
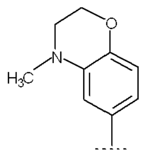
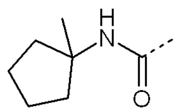
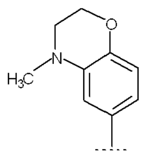
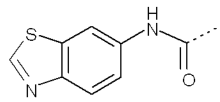
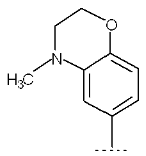
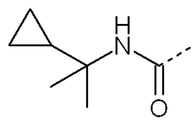
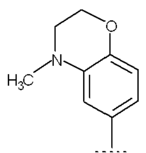
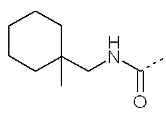
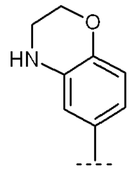
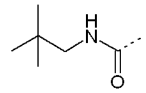
Cpd	R^3	R^{51a}	R^{51b}	t_R (min)	MS $(M+H)^+$
5001			H	8.8	511.2/ 513.2
5002			H	6.0/6.6*	522.3
5003			H	6.5/7.3*	548.4
5004			$-CF_3$	7.9/8.7*	616.3

TABLE 6



*presence of 2 inter-converting conformers by HPLC

Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
6001		-COOMe	8.2	467.1
6002			7.8	522.2
6003			7.4/7.5 *	506.2
6004			8.5/8.6	548.2
6005			8.5	548.2
6006			8.4	536.2

Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
6007			8.1	534.2
6008			6.2/6.4 *	537.3
6009			6.5/6.6 *	563.2
6010			6.3/6.5 *	549.2
6011			6.0/6.2 *	600.1
6012			6.3/6.5 *	549.2
6013			6.7/6.8 *	577.2
6014			5.3/5.8 *	523.2

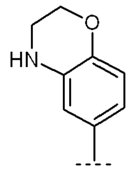
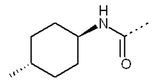
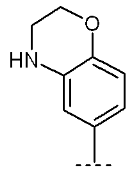
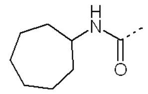
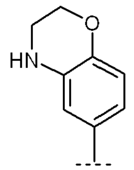
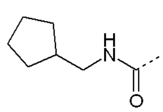
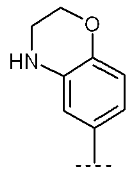
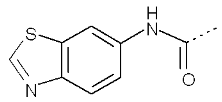
Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
6015			5.6/5.8 *	549.2
6016			5.7/6.2 *	549.2
6017			5.4/5.9 *	535.2
6018			5.0/5.6 *	586.1

TABLE 7

Antiviral potency

Compound #	EC_{50} nM
1005	19
1009	20
1011	59
1017	21
1018	180
1020	49
1102	17
1111	15
1113	7.7
1116	13
1119	17
1124	81
1127	4.5
1132	9.4
1141	26
1142	7.9
1143	21
1145	35

Compound #	EC_{50} nM
1437	0.75
1438	0.94
1439	4.0
1440	2.4
1441	4.9
1442	16
1443	7.1
1444	9.2
1445	1.9
1446	1.9
1447	0.38
1448	1.4
1449	1.8
1450	7.7
1451	1.7
1452	5.7
1453	2.1
1454	3.7

1146	17
1147	6.9
1152	15
1153	22
1154	27
1160	16
1161	27
1167	9.3
1192	8.3
1202	31
1208	8.9
1242	220
1256	8.1
1275	4.5
1276	68
1280	22
1283	140
1290	11
1293	24
1307	17
1311	26
1316	47

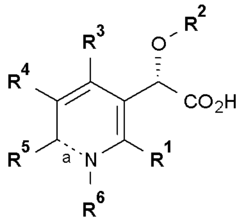
1455	4.0
1456	4.2
1457	4.0
1458	6.9
1459	4.0
1460	1.7
1461	2.5
1462	1.2
1463	2.1
1464	6.2
1465	11
1466	4.9
1467	4.3
1468	15
1469	0.61
1470	5.9
1471	2.4
2003	17
2005	19
3005	9.3
3009	24
4002	73
6001	89

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

What is claimed is:

1. A compound of Formula I and a racemate, enantiomer or diastereomer of a compound of formula (I):



(I)

wherein

$\mathbf{R^1}$ is (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{3-6})cycloalkyl, wherein the (C_{1-6})alkyl is optionally substituted with $-O(C_{1-6})$alkyl or $-S(C_{1-6})$alkyl;

$\mathbf{R^2}$ is (C_{1-8})alkyl or (C_{3-8})cycloalkyl, wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl;

$\mathbf{R^3}$ is aryl, wherein the aryl is optionally fused to one or more cycles, at least one of which is a heterocycle, to form a heteropolycycle, and wherein the aryl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and $-O(C_{1-6})$alkyl;

$\mathbf{R^4}$ is (C_{1-6})alkyl, -CN, halo, (C_{1-6})haloalkyl, (C_{3-5})cycloalkyl, or $-O(C_{1-6})$alkyl; and

a is a double bond, $\mathbf{R^6}$ is absent and $\mathbf{R^5}$ is $\mathbf{R^{51}}$ or $-(C_{1-3})$alkyl-$\mathbf{R^{51}}$; or

a is a single bond and $\mathbf{R^5}$ and $\mathbf{R^6}$ are joined, together with the atoms to which they are bonded, to form a 5-membered ring optionally having 1 to 3 further heteroatoms each independently selected from O, N and S, wherein the 5-membered ring is optionally substituted with 1 to 3 $\mathbf{R^{51}}$ substituents;

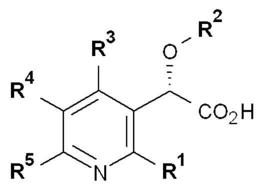
wherein $\mathbf{R^{51}}$ is in each case independently selected from $\mathbf{R^{52}}$, $-O\mathbf{R^{53}}$, $-N(\mathbf{R^{54}})\mathbf{R^{53}}$, $-C(=O)\mathbf{R^{52}}$, $-C(=O)O\mathbf{R^{53}}$, $-C(=O)N(\mathbf{R^{54}})\mathbf{R^{53}}$, $-OC(=O)N(\mathbf{R^{54}})\mathbf{R^{53}}$, $-N(\mathbf{R^{54}})C(=O)\mathbf{R^{52}}$, $-N(\mathbf{R^{54}})C(=O)N(\mathbf{R^{54}})\mathbf{R^{53}}$ and $-N(\mathbf{R^{54}})C(=O)O\mathbf{R^{53}}$; wherein

$\mathbf{R^{52}}$ is in each case independently selected from $\mathbf{R^{53}}$, (C_{2-8})alkenyl and (C_{2-8})alkynyl,

$\mathbf{R^{53}}$ is in each case independently selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

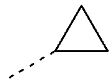
and
R^54 is in each case independently selected from H and (C_{1-3})alkyl;
wherein each of **R^52** and **R^53** is optionally substituted with 1 to 3 substituents each independently selected from **R^55**, halo, -CN, -O**R^56**, -S**R^56**, -SO**R^56**, $-SO_2$**R^56**, -N(**R^54**)**R^56**, -N(**R^54**)C(=O)**R^55**, -N(**R^54**)C(=O)N(**R^54**)**R^56**, -N(**R^54**)C(=O)O**R^56**, -OC(=O)N(**R^54**)**R^56**, -C(=O)**R^55**, -C(=O)O**R^56**, and -CON(**R^54**)**R^56**, wherein
R^55 is in each case independently selected from **R^56**, (C_{2-8})alkenyl and (C_{2-8})alkynyl, and
R^56 is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,
wherein each of **R^55** and **R^56** is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -OH, -O(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl, -N((C_{1-6})alkyl$)_2$ and -NH(C=O)(C_{1-6})alkyl;
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 thereof.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

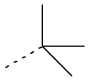
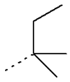
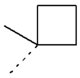


wherein **R^1**, **R^2**, **R^3**, **R^4** and **R^5** are as defined in claim 1.

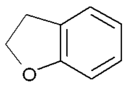
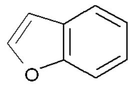
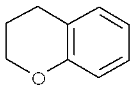
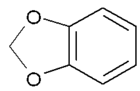
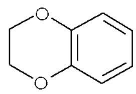
3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein **R^1** is selected from:

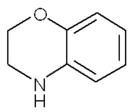
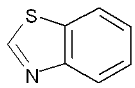
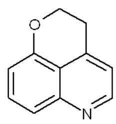
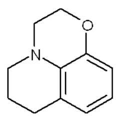
$-CH_3$, $-CH_2OMe$, $-CH_2OEt$, $-CH_2SMe$, $-CH=CH_2$ and  .

4. The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein **R**^{2} is selected from:

 ,  and  .

5. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein **R**^{3} is phenyl or a heteropolycycle selected from:

 ,  ,  ,  ,  ,

 ,  ,  and  ; wherein the phenyl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and $-O(C_{1-6})$alkyl.

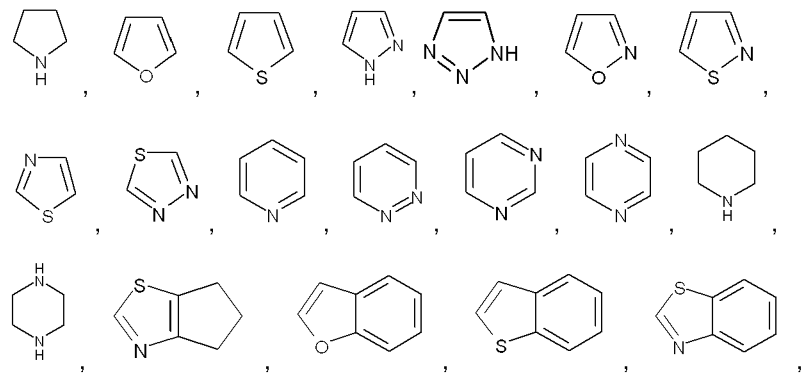
6. The compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein **R**^{4} is (C_{1-6})alkyl, -CN, halo or (C_{1-6})haloalkyl.

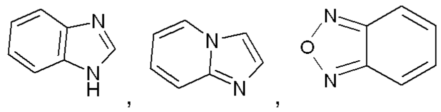
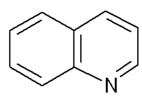
7. The compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein **R**^{4} is $-CH_3$.

8. The compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein **a** is a double bond, **R**^{6} is absent and **R**^{5} is **R**^{51} or $-(C_{1-3})$alkyl-**R**^{51};
wherein **R**^{51} is selected from **R**^{52}, -O**R**^{53}, -C(=O)**R**^{52}, --C(=O)O**R**^{53}, -C(=O)N(**R**^{54})**R**^{53}, -N(**R**^{54})C(=O)**R**^{52}, -N(**R**^{54})C(=O)N(**R**^{54})**R**^{53} and -N(**R**^{54})C(=O)O**R**^{53}; wherein
R^{52} is selected from **R**^{53} and (C_{2-8})alkenyl, and

R^{53} is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



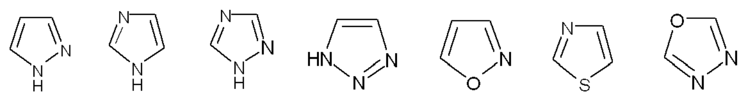
 and  ; and

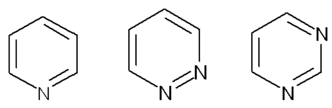
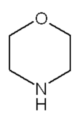
R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of **R**^{52} and **R**^{53} is optionally substituted with 1 to 3 substituents each independently selected from **R**^{56}, halo, -CN, -O**R**^{56}, -S**R**^{56}, $-SO_2$**R**^{56}, -N(**R**^{54})**R**^{56} and -CON(**R**^{54})**R**^{56}, wherein

R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

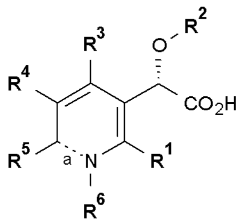
wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



 and  ;

wherein **R**^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, $-O(C_{1-6})$alkyl, $-N((C_{1-6})alkyl)_2$ and $-NH(C=O)(C_{1-6})$alkyl.

9. A compound and a racemate, enantiomer or diastereomer of a compound having the formula:



wherein

R^1 is (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{3-6})cycloalkyl, wherein the (C_{1-6})alkyl is optionally substituted with –O(C_{1-6})alkyl or -S(C_{1-6})alkyl;

R^2 is (C_{1-8})alkyl or (C_{3-8})cycloalkyl, wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl;

R^3 is aryl, wherein the aryl is optionally fused to one or more cycles, at least one of which is a heterocycle, to form a heteropolycycle, and wherein the aryl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and -O(C_{1-6})alkyl;

R^4 is (C_{1-6})alkyl, -CN, halo, (C_{1-6})haloalkyl, (C_{3-5})cycloalkyl, or –O(C_{1-6})alkyl; and

a is a double bond, **R**^{6} is absent and **R**^{5} is **R**^{51} or -(C_{1-3})alkyl-**R**^{51}; or

a is a single bond and **R**^{5} and **R**^{6} are joined, together with the atoms to which they are bonded, to form a 5-membered ring optionally having 1 to 3 further heteroatoms each independently selected from O, N and S, wherein the 5-membered ring is optionally substituted with 1 to 3 **R**^{51} substituents;

wherein **R**^{51} is in each case independently selected from **R**^{52}, -O**R**^{53}, -N(**R**^{54})**R**^{53}, -C(=O)**R**^{52}, -C(=O)O**R**^{53}, -C(=O)N(**R**^{54})**R**^{53}, -OC(=O)N(**R**^{54})**R**^{53}, -N(**R**^{54})C(=O)**R**^{52}, -N(**R**^{54})C(=O)N(**R**^{54})**R**^{53} and -N(**R**^{54})C(=O)O**R**^{53}; wherein

R^{52} is in each case independently selected from **R**^{53}, (C_{2-8})alkenyl and (C_{2-8})alkynyl,

R^{53} is in each case independently selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{5-14})spirocycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of **R**^{52} and **R**^{53} is optionally substituted with 1 to 3 substituents each independently selected from **R**^{55}, halo, -CN, -O**R**^{56}, -S**R**^{56},

-SO**R**^{56}, -SO$_2$**R**^{56}, -N(**R**^{54})**R**^{56}, -N(**R**^{54})C(=O)**R**^{55}, -N(**R**^{54})C(=O)N(**R**^{54})**R**^{56}, -N(**R**^{54})C(=O)O**R**^{56}, -OC(=O)N(**R**^{54})**R**^{56}, -C(=O)**R**^{55}, -C(=O)O**R**^{56}, and -CON(**R**^{54})**R**^{56}, wherein

R^{55} is in each case independently selected from **R**^{56}, (C$_{2-8}$)alkenyl and (C$_{2-8}$)alkynyl, and

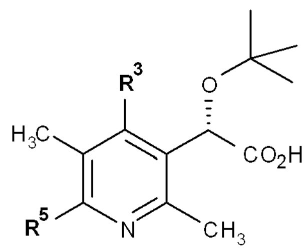
R^{56} is in each case independently selected from H, (C$_{1-8}$)alkyl, (C$_{3-8}$)cycloalkyl, (C$_{3-8}$)cycloalkyl-(C$_{1-6}$)alkyl-, aryl, aryl-(C$_{1-6}$)alkyl-, **Het**, and **Het**-(C$_{1-6}$)alkyl-,

wherein each of **R**^{55} and **R**^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C$_{1-6}$)alkyl, (C$_{1-6}$)haloalkyl, halo, -OH, -O(C$_{1-6}$)alkyl, -NH$_2$, -NH(C$_{1-6}$)alkyl, -N((C$_{1-6}$)alkyl)$_2$ and -NH(C=O)(C$_{1-6}$)alkyl;

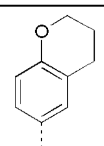
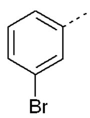
wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected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

or a salt thereof.

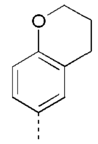
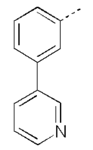
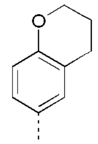
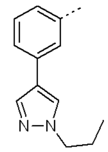
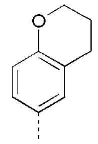
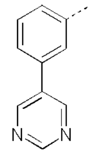
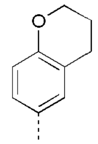
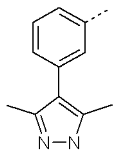
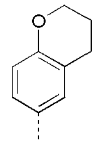
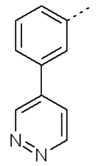
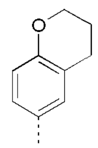
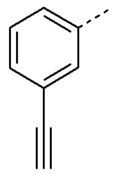
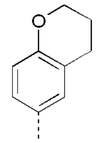
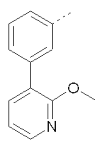
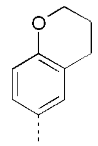
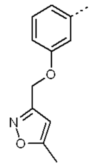
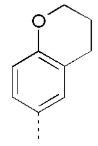
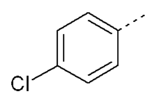
10. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

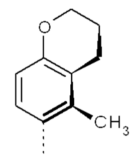
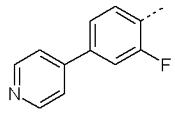
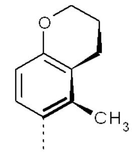
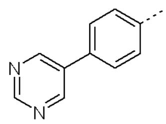
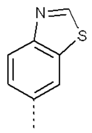
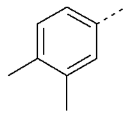
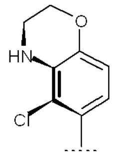
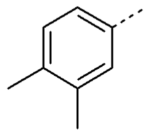
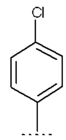
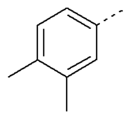
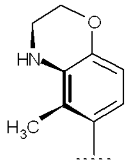
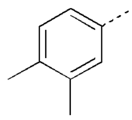
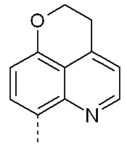
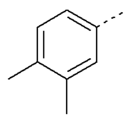
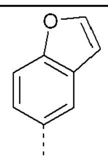
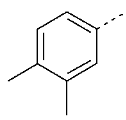
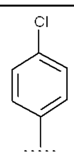
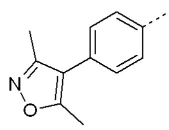


wherein **R**^{3} and **R**^{5} are defined as:

R^3	**R**^{5}
	

;

R^3	R^5	
		;
		;
		;
		;
		;
		;
		;
		;
		;

R^3	R^5	
		;
		;
		;
		;
		;
		;
		;
		;
		;

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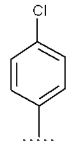
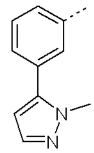
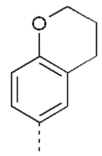
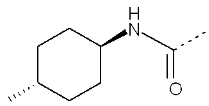
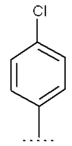
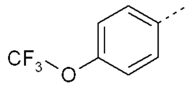
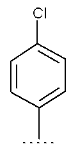
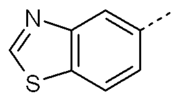
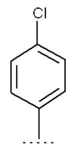
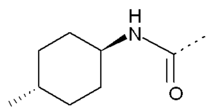
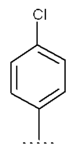
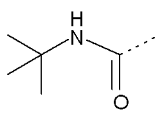
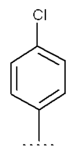
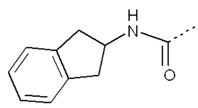
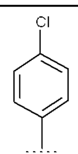
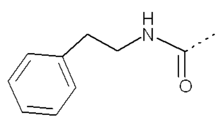
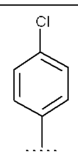
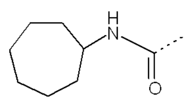
		;
		;
		;
		;
		;
		;
		;
		;
		;

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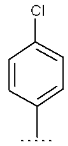
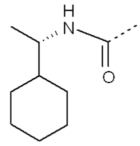
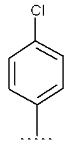
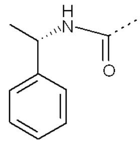
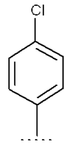
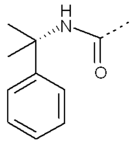
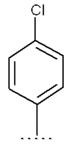
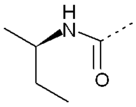
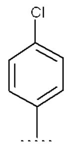
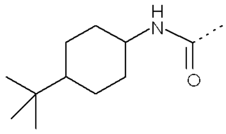
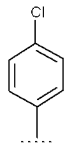
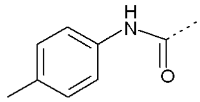
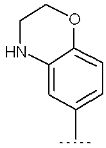
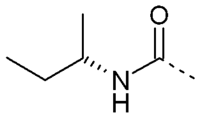
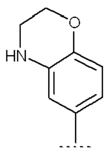
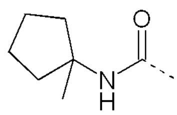
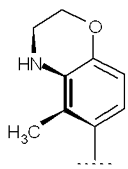
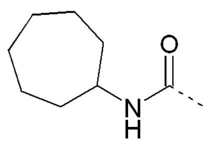
		;
		;
		;
		;
		;
		;
		;
		;
		;

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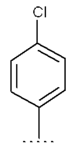
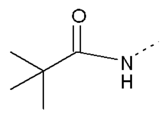
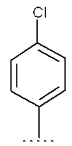
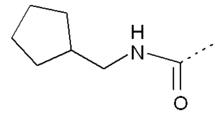
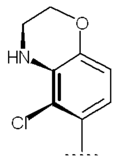
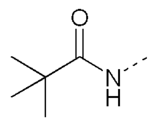
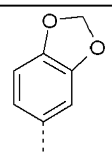
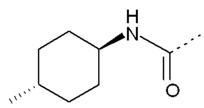
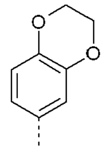
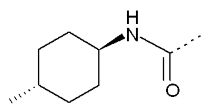
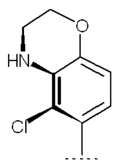
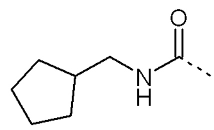
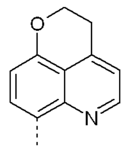
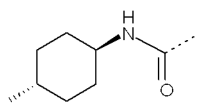
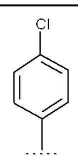
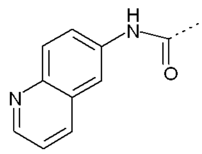
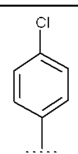
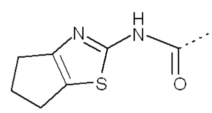
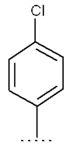
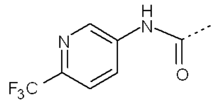
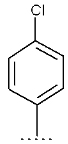
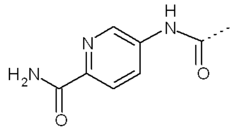
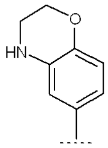
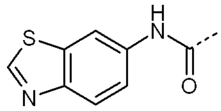
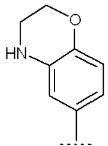
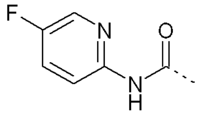
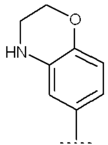
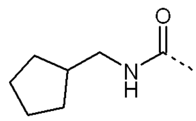
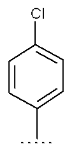
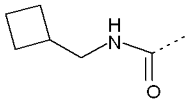
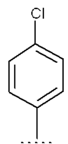
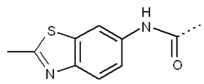
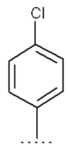
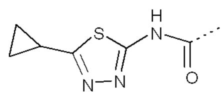
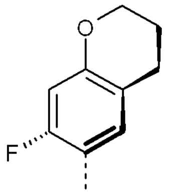
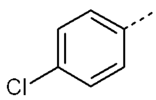
		;
		;
		;
		;
		;
		;
		;
		;
		;

R³	R⁵	
Cl	H N N O F₃C	;
Cl	H N N O H₂N O	;
O HN	H N S O N	;
O HN	F N O N H	;
O HN	O N H	;
Cl	H N O	;
Cl	H S N N O	;
Cl	H S N N–N O	;
O F	Cl	;

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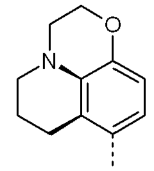
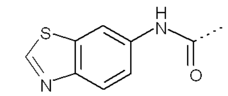
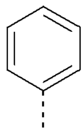
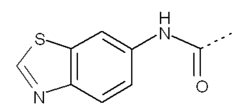
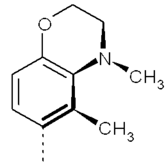
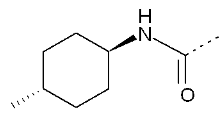
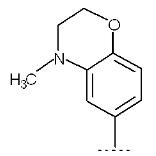
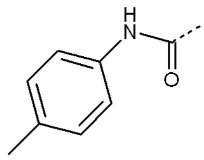
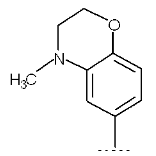
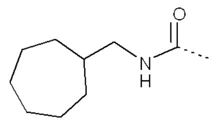
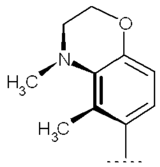
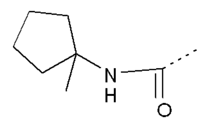
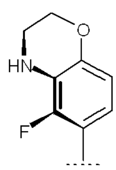
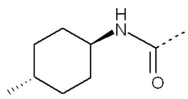
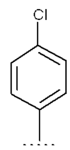
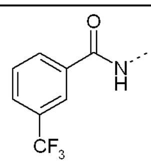
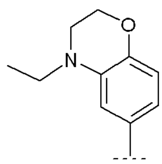
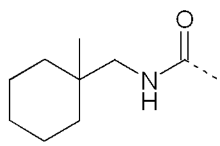
		;
		;
		;
		;
		;
		;
		;
		;
		;

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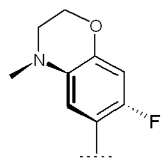
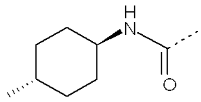
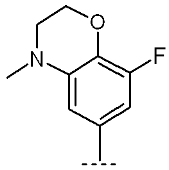
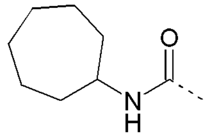
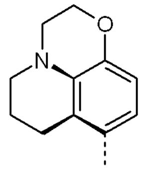
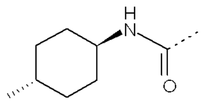
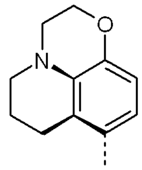
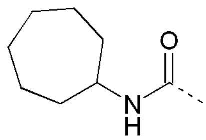
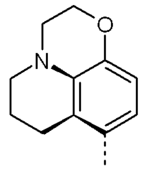
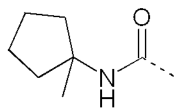
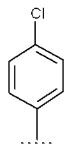
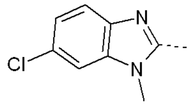
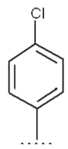
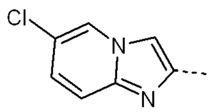
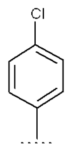
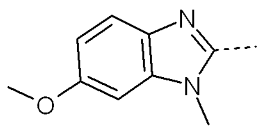
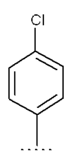
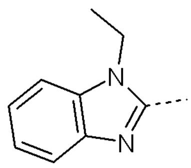
		;
		;
		;
		;
		;
		;
		;
		;
		;

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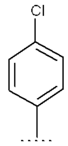
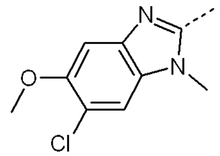
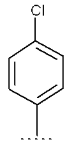
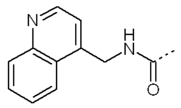
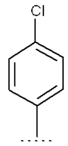
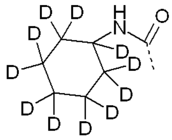
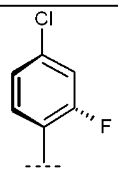
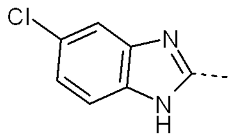
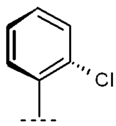
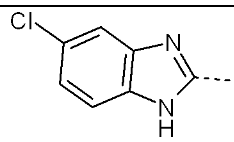
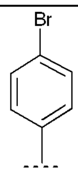
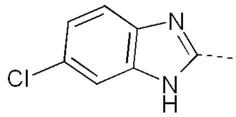
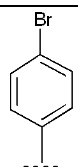
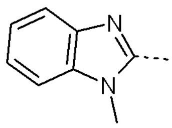
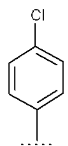
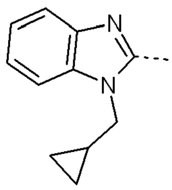
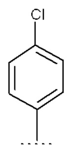
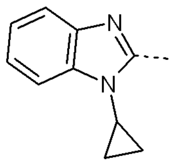
		;
		;
		;
		;
		;
		;
		;
		;
		;

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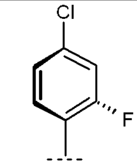
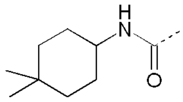
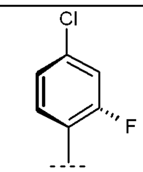
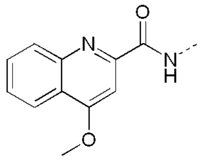
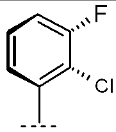
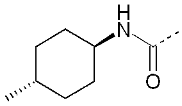
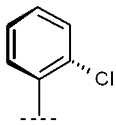
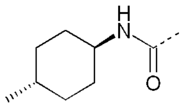
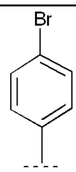
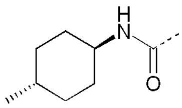
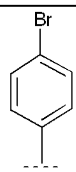
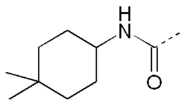
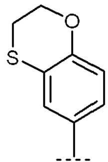
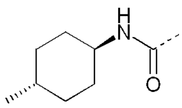
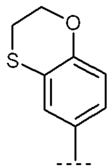
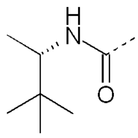
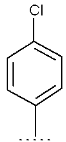
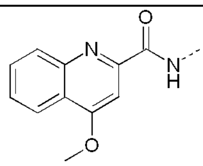
		;
		;
		;
		;
		;
		;
		;
		;
		;

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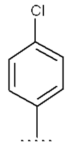
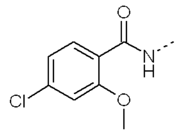
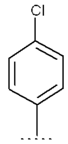
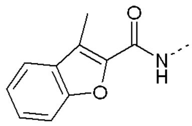
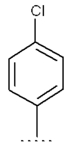
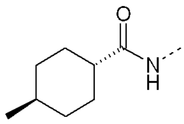
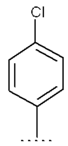
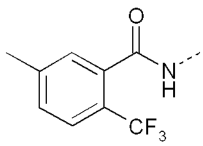
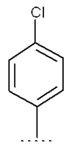
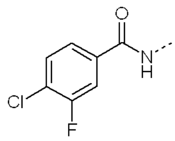
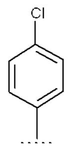
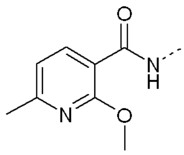
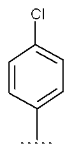
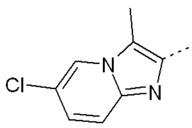
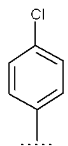
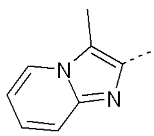
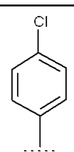
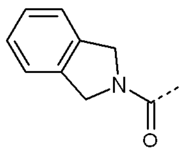
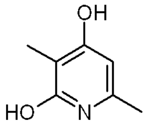
		;
		;
		;
		;
		;
		;
		;
		; and
		.

11. A compound represented by a formula selected from the group consisting of: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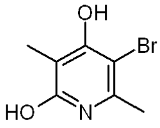
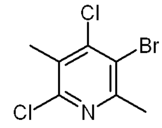

2d ,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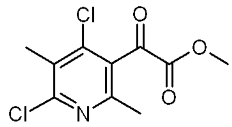
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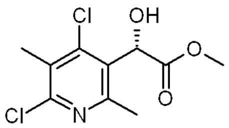
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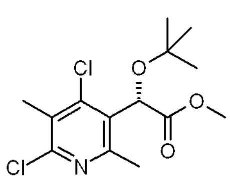
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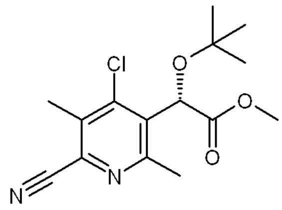
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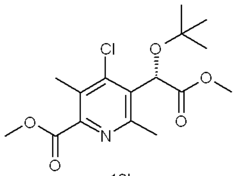
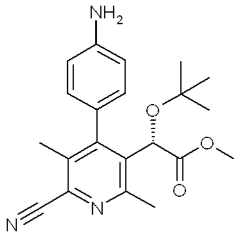

10b ,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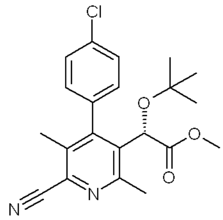
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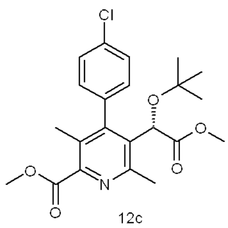
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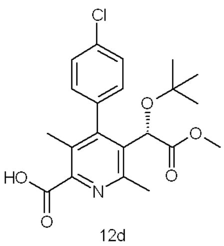
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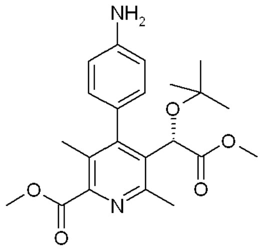
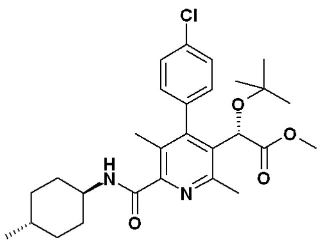

36a and


37a .

12. The compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, as a medicament.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof; and one or more pharmaceutically acceptable carriers.

14. The pharmaceutical composition according to claim 13 further comprising at least one other antiviral agent.

15. Use of a compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for the treatment of an HIV infection in a human being having or at risk of having the infection.