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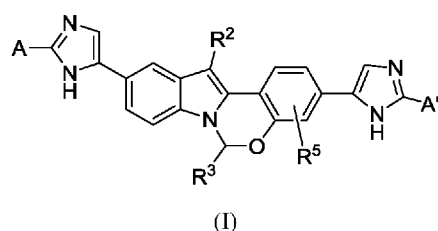
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(54) Title: CHROMANE-SUBSTITUED TETRACYCLIC COMPOUNDS AND USES THEREOF FOR TREATMENT OF VIRAL DISEASES



(57) Abstract: Disclosed are novel chromane-substituted tetracyclic compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein A, A', R², R³, R⁴ and R⁵ are as defined in the description. Also disclosed are compositions comprising a chromane-substituted tetracyclic compound, and methods of using the chromane-substituted tetracyclic compounds for treating or preventing HCV infection in a patient.

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CHROMANE-SUBSTITUED TETRACYCLIC COMPOUNDS AND USES THEREOF FOR TREATMENT OF VIRAL DISEASES

FIELD OF THE INVENTION

10 The present invention relates to novel Chromane-Substituted
Tetracyclic Compounds, compositions comprising a Chromane-Substituted
Tetracyclic Compound, and methods of using the Chromane-Substituted Tetracyclic
Compounds for treating or preventing HCV infection in a patient.

15 **BACKGROUND OF THE INVENTION**

Hepatitis C virus (HCV) is a major human pathogen. A substantial
fraction of these HCV-infected individuals develop serious progressive liver disease,
including cirrhosis and hepatocellular carcinoma, which are often fatal.

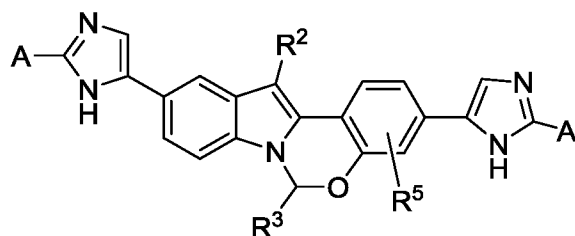
Recent attention has been focused toward the identification of
20 inhibitors of HCV NS5A. HCV NS5A is a 447 amino acid phosphoprotein which
lacks a defined enzymatic function. It runs as 56kD and 58kD bands on gels
depending on phosphorylation state (Tanji, *et al. J. Virol.* 69:3980-3986 (1995)).
HCV NS5A resides in replication complex and may be responsible for the switch
from replication of RNA to production of infectious virus (Huang, Y, *et al., Virology*
25 364:1-9 (2007)).

Multicyclic HCV NS5A inhibitors have been reported. See U.S. Patent
Publication Nos. US20080311075, US20080044379, US20080050336, US20080044380,
US20090202483 and US2009020478. HCV NS5A inhibitors having fused tricyclic
moieties are disclosed in International Patent Publication Nos. WO 10/065681, WO
30 10/065668, and WO 10/065674.

Other HCV NS5A inhibitors and their use for reducing viral load in
HCV infected humans have been described in U.S. Patent Publication No.
US20060276511.

35 **SUMMARY OF THE INVENTION**

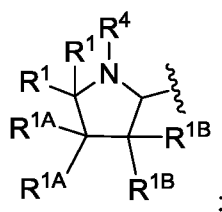
In one aspect, the present invention provides Compounds of Formula



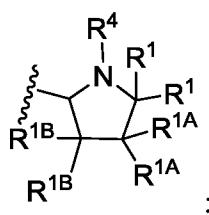
(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is:



A' is:



each occurrence of R^1 is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkyl, $-O$ - C_1 - C_6 alkyl, $-N(R^9)_2$, $-O$ -(C_1 - C_6 haloalkyl), and halo;

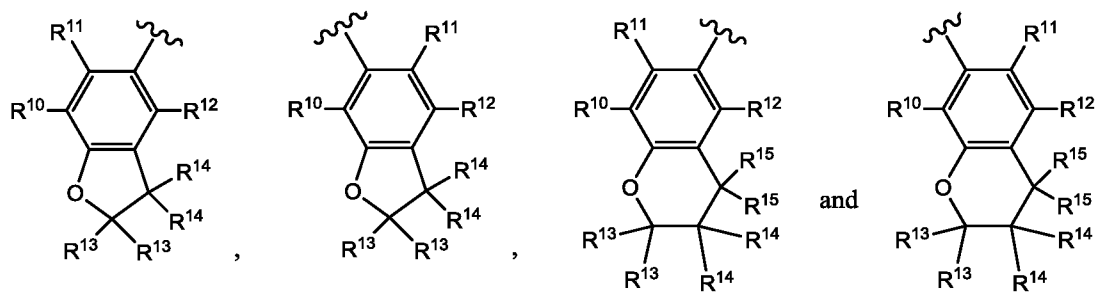
each occurrence of R^{1A} is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkyl, $-O$ - C_1 - C_6 alkyl, $-N(R^9)_2$, $-O$ -(C_1 - C_6 haloalkyl), and halo, or one R^{1A} group and an R^1 group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused C_3 - C_7 cycloalkyl group, or two R^{1A} groups that are attached to the same carbon atom, and the common carbon atom to which they are attached, can combine to form a spirocyclic C_3 - C_7 cycloalkyl group;

each occurrence of R^{1B} is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkyl, $-O$ - C_1 - C_6 alkyl, $-N(R^9)_2$, $-O$ -(C_1 - C_6 haloalkyl) and halo, or an R^{1B} group and an R^{1A} group that are attached to the same ring, together with the carbon atoms to which they are attached, can combine to form a fused C_3 - C_7 cycloalkyl group, or an R^{1B} group and an R^1 group that are attached to the

- 5 same ring, can combine to form a bridging group having the formula $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$;

R^2 is selected from H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, phenyl and halo;

R^3 is selected from:



- 10 each occurrence of R^4 is independently selected from $-\text{C}(\text{O})-\text{C}(\text{R}^7)_2\text{NHC}(\text{O})\text{O}-\text{R}^8$ and $-\text{C}(\text{O})-\text{C}(\text{R}^7)_2-\text{N}(\text{R}^6)_2$

- R^5 represents up to 3 optional substituents, each independently selected from halo, $-\text{CN}$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, 4 to 6-membered monocyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, $\text{C}_6\text{-C}_{10}$ aryl, benzyl and $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, wherein said $\text{C}_3\text{-C}_7$ cycloalkyl group, said 4 to 6-membered monocyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group, said $\text{C}_6\text{-C}_{10}$ aryl group, or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, $-\text{CN}$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{O}-\text{C}_1\text{-C}_6$ alkyl, $-(\text{C}_1\text{-C}_6 \text{ alkylene})-\text{O}-\text{C}_1\text{-C}_6$ alkyl and $-\text{O}-(\text{C}_1\text{-C}_6 \text{ haloalkyl})$;

each occurrence of R^6 is independently selected from H, $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_3\text{-C}_7$ cycloalkyl, wherein two R^6 groups, together with the nitrogen atom to which they are attached, can combine to form a 4 to 8-membered monocyclic heterocycloalkyl;

- 25 each occurrence of R^7 is independently selected from H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, phenyl, 4 to 8-membered monocyclic heterocycloalkyl, 6 to 10-membered bicyclic heterocycloalkyl and $\text{C}_3\text{-C}_7$ cycloalkyl, wherein said 4 to 8-membered monocyclic heterocycloalkyl group, said 6 to 10-membered bicyclic heterocycloalkyl group and said $\text{C}_3\text{-C}_7$ cycloalkyl group can be optionally substituted with up to 5 groups, each independently selected from halo, $-\text{CN}$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-\text{O}-\text{C}_1\text{-C}_6$ alkyl, $-\text{N}(\text{R}^9)_2$ and $-\text{O}-(\text{C}_1\text{-C}_6 \text{ haloalkyl})$, and wherein said $\text{C}_3\text{-C}_7$ cycloalkyl group can be optionally fused to a 4 to 6-membered monocyclic heterocycloalkyl group, and wherein said 4 to 8-membered monocyclic

- 5 heterocycloalkyl group and said C₃-C₇ cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic C₃-C₆ cycloalkyl group; and wherein said C₃-C₇ cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic 3 to 6-membered monocyclic heterocycloalkyl group, and wherein two R⁷ groups, that are attached to a common carbon atom, together with the common carbon atom to which
- 10 they are attached, can combine to form a spirocyclic C₃-C₇ cycloalkyl group;
each occurrence of R⁸ is independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl and C₆-C₁₀ aryl;
each occurrence of R⁹ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and C₆-C₁₀ aryl;
- 15 R¹⁰ is selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo;
R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo;
R¹² is selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo;
each occurrence of R¹³ is independently selected from H, C₁-C₆ alkyl and C₃-C₇ cycloalkyl, or both R¹³ groups and the common carbon atom to which they
- 20 are each attached, can combine to form a spirocyclic C₃-C₇ cycloalkyl group;
each occurrence of R¹⁴ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo; or both R¹⁴ groups and the common carbon atom to which they are each attached, join to form a spirocyclic C₃-C₇ cycloalkyl group; or an R¹⁴ group and R¹³ group, together with the carbon atoms to which they are each attached,
- 25 join to form a fused C₃-C₇ cycloalkyl group; or an R¹⁴ group and R¹⁵ group, together with the carbon atoms to which they are each attached, can combine to form a fused C₃-C₇ cycloalkyl group; and
each occurrence of R¹⁵ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo, or both R¹⁵ groups and the common carbon atom to which
- 30 they are each attached, can combine to form a spirocyclic C₃-C₇ cycloalkyl group.

The Compounds of Formula (I) (also referred to herein as the “Chromane-Substituted Tetracyclic Compounds”) and pharmaceutically acceptable salts thereof can be useful, for example, for inhibiting HCV viral replication or

35 replicon activity, and for treating or preventing HCV infection in a patient. Without being bound by any specific theory, it is believed that the Chromane-Substituted Tetracyclic Compounds inhibit HCV viral replication by inhibiting HCV NS5A.

5 Accordingly, the present invention provides methods for treating or preventing HCV infection in a patient, comprising administering to the patient an effective amount of at least one Chromane-Substituted Tetracyclic Compound.

10 The details of the invention are set forth in the accompanying detailed description below.

 Although any methods and materials similar to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing
15 description, examples and appended claims.

Definitions and Abbreviations

 The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and
20 except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name and an ambiguity exists between the structure and the name, the structure predominates. These
25 definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "-O-alkyl," etc...

 As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

30 A "patient" is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a chimpanzee.

 The term "effective amount" as used herein, refers to an amount of Chromane-Substituted Tetracyclic Compound and/or an additional therapeutic agent, or a composition thereof that is effective in producing the desired therapeutic,
35 ameliorative, inhibitory or preventative effect when administered to a patient suffering from a viral infection or virus-related disorder. In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are

- 5 together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The term "preventing," as used herein with respect to an HCV viral infection or HCV-virus related disorder, refers to reducing the likelihood of HCV infection.

- 10 The term "alkyl," as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond. An alkyl group may be straight or branched and contain from about 1 to about 20 carbon atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In different embodiments, an alkyl group contains from 1 to 6 carbon atoms (C₁-C₆ alkyl) or from about 1 to about 4 carbon atoms (C₁-C₄ alkyl). Non-limiting examples of
15 alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH₂, -NH(alkyl), -N(alkyl)₂, NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. In one
20 embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched. Unless otherwise indicated, an alkyl group is unsubstituted.

- 25 The term "alkenyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and having one of its hydrogen atoms replaced with a bond. An alkenyl group may be straight or branched and contain from about 2 to about 15 carbon atoms. In one embodiment, an alkenyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples
30 of alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkenyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH₂, -
35 NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. The term "C₂-C₆ alkenyl" refers to an

- 5 alkenyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkenyl group is unsubstituted.

The term "alkynyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and having one of its hydrogen atoms replaced with a bond. An alkynyl group may be straight or branched and contain from about 2 to about 15 carbon atoms. In one embodiment, an alkynyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkynyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butylnyl and 3-methylbutynyl. An alkynyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and -C(O)O-alkyl. The term "C₂-C₆ alkynyl" refers to an alkynyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkynyl group is unsubstituted.

The term "alkylene," as used herein, refers to an alkyl group, as defined above, wherein one of the alkyl group's hydrogen atoms has been replaced with a bond. Non-limiting examples of alkylene groups include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH(CH₃)CH₂CH₂-, -CH(CH₃)- and -CH₂CH(CH₃)CH₂-. In one embodiment, an alkylene group has from 1 to about 6 carbon atoms. In another embodiment, an alkylene group is branched. In another embodiment, an alkylene group is linear. In one embodiment, an alkylene group is -CH₂-. The term "C₁-C₆ alkylene" refers to an alkylene group having from 1 to 6 carbon atoms.

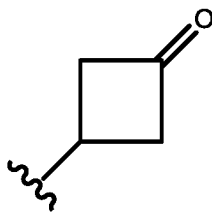
30 The term "aryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an aryl group contains from about 6 to about 10 carbon atoms. An aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, an aryl group can be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of aryl groups include phenyl and naphthyl. In one embodiment, an aryl group is phenyl. Unless otherwise indicated, an aryl group is unsubstituted.

5 The term "cycloalkyl," as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkyl contains from about 3 to about 7 ring atoms. In another embodiment, a cycloalkyl contains from about 5 to about 6 ring atoms. The

10 term "cycloalkyl" also encompasses a cycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalinyl, norbornyl and adamantyl. A cycloalkyl group can be optionally

15 substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, a cycloalkyl group is unsubstituted. The term "3 to 6-membered cycloalkyl" refers to a cycloalkyl group having from 3 to 6 ring carbon atoms. A ring carbon atom of a cycloalkyl group may be functionalized as a carbonyl group. Unless otherwise indicated, a cycloalkyl group

20 is unsubstituted. An illustrative example of such a cycloalkyl group (also referred to herein as a "cycloalkanoyl" group) includes, but is not limited to, cyclobutanoyl:



 The term "cycloalkenyl," as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from about 4 to about 10 ring carbon

25 atoms and containing at least one endocyclic double bond. In one embodiment, a cycloalkenyl contains from about 4 to about 7 ring carbon atoms. In another embodiment, a cycloalkenyl contains 5 or 6 ring atoms. Non-limiting examples of monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. A cycloalkenyl group can be optionally substituted with one or more

30 "ring system substituents" which may be the same or different, and are as defined herein below. A ring carbon atom of a cycloalkenyl group may be functionalized as a carbonyl group. In one embodiment, a cycloalkenyl group is cyclopentenyl. In another embodiment, a cycloalkenyl group is cyclohexenyl. The term "4 to 6-

5 membered cycloalkenyl" refers to a cycloalkenyl group having from 4 to 6 ring carbon atoms. Unless otherwise indicated, a cycloalkenyl group is unsubstituted.

The term "halo," as used herein, means -F, -Cl, -Br or -I.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been
10 replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include -CH₂F, -CHF₂, -CF₃, -CH₂Cl and -CCl₃. The term "C₁-C₆ haloalkyl" refers to a haloalkyl group having from 1 to 6 carbon atoms.

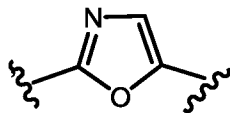
15 The term "hydroxyalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with an -OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of hydroxyalkyl groups include -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH and -CH₂CH(OH)CH₃. The term "C₁-C₆
20 hydroxyalkyl" refers to a hydroxyalkyl group having from 1 to 6 carbon atoms.

The term "heteroaryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In
25 another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroaryl group is bicyclic and had 9 or 10 ring atoms. A heteroaryl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroaryl group is joined via a ring carbon atom, and any nitrogen atom of a
30 heteroaryl can be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, which is fused to a benzene ring. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl,
35 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxaliny, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, benzimidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolyl,

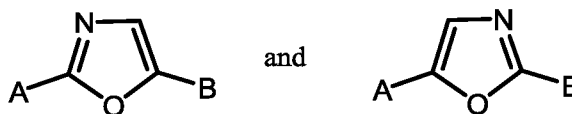
5 benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like, and all isomeric forms thereof. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a heteroaryl group is a 5-membered heteroaryl. In another embodiment, a heteroaryl group is a 6-membered heteroaryl. In another embodiment, a heteroaryl group comprises a 5- to 6-membered heteroaryl group fused to a benzene ring. Unless otherwise indicated, a heteroaryl group is unsubstituted.

The term "heteroarylene," as used herein, refers to a bivalent group derived from an heteroaryl group, as defined above, by removal of a hydrogen atom from a ring carbon or ring heteroatom of a heteroaryl group. A heteroarylene group can be derived from a monocyclic or polycyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms are each independently O, N or S and the remaining ring atoms are carbon atoms. A heteroarylene group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroarylene group is joined via a ring carbon atom or by a nitrogen atom with an open valence, and any nitrogen atom of a heteroarylene can be optionally oxidized to the corresponding N-oxide. The term "heteroarylene" also encompasses a heteroarylene group, as defined above, which is fused to a benzene ring. Non-limiting examples of heteroarylenes include pyridylene, pyrazinylene, furanylene, thienylene, pyrimidinylene, pyridonylene (including those derived from N-substituted pyridonyls), isoxazolylenes, isothiazolylenes, oxazolylenes, oxadiazolylenes, thiazolylenes, pyrazolylenes, thiophenylene, furazanylene, pyrrolylene, triazolylenes, 1,2,4-thiadiazolylenes, pyrazinylene, pyridazinylene, quinoxalinylenes, phthalazinylene, oxindolylene, imidazo[1,2-a]pyridinylenes, imidazo[2,1-b]thiazolylenes, benzofurazanylene, indolylene, azaindolylene, benzimidazolylenes, benzothienylene, quinolinylenes, imidazolylenes, benzimidazolylenes, thienopyridylene, quinazolinylene, thienopyrimidylene, pyrrolopyridylene, imidazopyridylene, isoquinolinylenes, benzoazaindolylene, 1,2,4-triazinylene, benzothiazolylenes and the like, and all isomeric forms thereof. The term "heteroarylene" also refers to partially saturated heteroarylene moieties such as, for example, tetrahydroisoquinolylene, tetrahydroquinolylene, and the like. A heteroarylene group is divalent and unless specified otherwise, either available bond on a heteroarylene ring can connect to

- 5 either group flanking the heteroarylene group. For example, the group "A-heteroarylene-B," wherein the heteroarylene group is:



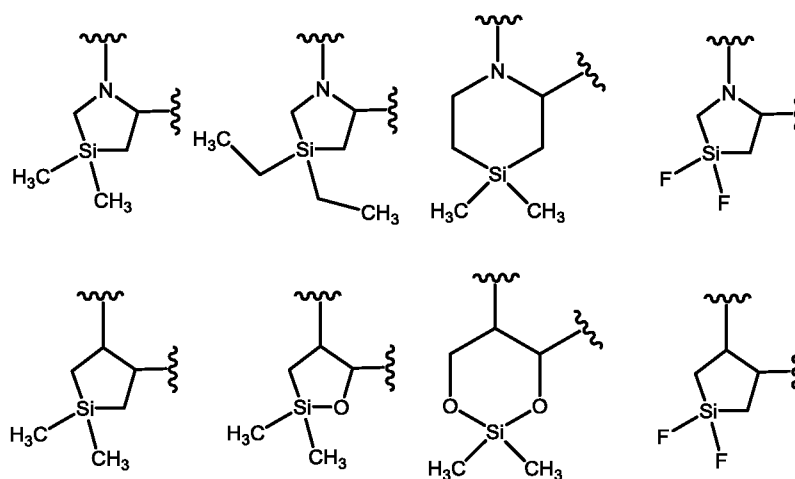
is understood to represent both:



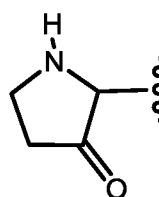
- 10 In one embodiment, a heteroarylene group is a monocyclic heteroarylene group or a bicyclic heteroarylene group. In another embodiment, a heteroarylene group is a monocyclic heteroarylene group. In another embodiment, a heteroarylene group is a bicyclic heteroarylene group. In still another embodiment, a heteroarylene group has from about 5 to about 10 ring atoms. In another embodiment, a heteroarylene group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroarylene group is bicyclic and has 9 or 10 ring atoms. In another embodiment, a heteroarylene group is a 5-membered monocyclic heteroarylene. In another embodiment, a heteroarylene group is a 6-membered monocyclic heteroarylene. In another embodiment, a bicyclic heteroarylene group comprises a 5 or 6-membered monocyclic heteroarylene group fused to a benzene ring. Unless otherwise indicated, a heteroarylene group is unsubstituted.

- The term "heterocycloalkyl," as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 11 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S, N or Si, and the remainder of the ring atoms are carbon atoms. A heterocycloalkyl group can be joined via a ring carbon, ring silicon atom or ring nitrogen atom. In one embodiment, a heterocycloalkyl group is monocyclic and has from about 3 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is monocyclic has from about 4 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is bicyclic and has from about 7 to about 11 ring atoms. In still another embodiment, a heterocycloalkyl group is monocyclic and has 5 or 6 ring atoms. In one embodiment, a heterocycloalkyl group is monocyclic. In another embodiment, a heterocycloalkyl group is bicyclic. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any -NH group in a heterocycloalkyl ring may exist protected such as,

- 5 for example, as an -N(BOC), -N(Cbz), -N(Tos) group and the like; such protected heterocycloalkyl groups are considered part of this invention. Unless otherwise indicated, a heterocycloalkyl group is unsubstituted. The term "heterocycloalkyl" also encompasses a heterocycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. A heterocycloalkyl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. The nitrogen or sulfur atom of the heterocycloalkyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include oxetanyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 10 thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, delta-lactam, delta-lactone, silacyclopentane, silapyrrolidine and the like, and all isomers thereof. Non-limiting illustrative examples of a silyl-containing heterocycloalkyl group include:



- 20 A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is:



- In one embodiment, a heterocycloalkyl group is a 5-membered monocyclic heterocycloalkyl. In another embodiment, a heterocycloalkyl group is a 6-membered monocyclic heterocycloalkyl. The term "3 to 6-membered monocyclic cycloalkyl" refers to a monocyclic heterocycloalkyl group having from 3 to 6 ring 25

5 atoms. The term “4 to 6-membered monocyclic cycloalkyl” refers to a monocyclic heterocycloalkyl group having from 4 to 6 ring atoms. The term “7 to 11-membered bicyclic heterocycloalkyl” refers to a bicyclic heterocycloalkyl group having from 7 to 11 ring atoms.

The term “heterocycloalkenyl,” as used herein, refers to a
10 heterocycloalkyl group, as defined above, wherein the heterocycloalkyl group contains from 4 to 10 ring atoms, and at least one endocyclic carbon-carbon or carbon-nitrogen double bond. A heterocycloalkenyl group can be joined via a ring carbon or ring nitrogen atom. In one embodiment, a heterocycloalkenyl group has from 4 to 6 ring atoms. In another embodiment, a heterocycloalkenyl group is
15 monocyclic and has 5 or 6 ring atoms. In another embodiment, a heterocycloalkenyl group is bicyclic. A heterocycloalkenyl group can optionally substituted by one or more ring system substituents, wherein “ring system substituent” is as defined above. The nitrogen or sulfur atom of the heterocycloalkenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. A ring carbon atom of a
20 heterocycloalkenyl group may be functionalized as a carbonyl group. Non-limiting examples of heterocycloalkenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazoliny, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-
25 dihydro-2H-pyranly, dihydrofuranyl, fluoro-substituted dihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranly, and the like and the like. In one embodiment, a heterocycloalkenyl group is a 5-membered heterocycloalkenyl. In another embodiment, a heterocycloalkenyl group is a 6-membered heterocycloalkenyl. The term “4 to 6-membered heterocycloalkenyl”
30 refers to a heterocycloalkenyl group having from 4 to 6 ring atoms. Unless otherwise indicated, a heterocycloalkenyl group is unsubstituted.

The term “substituted” means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not
35 exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By “stable compound” or “stable structure” is meant a compound that is

5 sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "in substantially purified form," as used herein, refers to the physical state of a compound after the compound is isolated from a synthetic process (e.g., from a reaction mixture), a natural source, or a combination thereof. The term
10 "in substantially purified form," also refers to the physical state of a compound after the compound is obtained from a purification process or processes described herein or well-known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well-known to the skilled artisan.

15 It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the
20 protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

When any substituent or variable (e.g., R¹, m, etc.) occurs more than
25 one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results from combination of the specified ingredients in the specified
30 amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American
35 Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g., a drug precursor) that is transformed *in vivo* to provide a Chromane-Substituted Tetracyclic Compound or a pharmaceutically acceptable salt or solvate of

5 the compound. The transformation may occur by various mechanisms (*e.g.*, by metabolic or chemical processes), such as, for example, through hydrolysis in blood.

For example, if a Chromane-Substituted Tetracyclic Compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example,
 10 (C₁-C₈)alkyl, (C₂-C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 6 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di (C₁-
 15 C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl, and the like.

Similarly, if a Chromane-Substituted Tetracyclic Compound contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C₁-
 25 C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkyl, α-amino(C₁-C₄)alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring
 30 L-amino acids, -P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a Chromane-Substituted Tetracyclic Compound incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen
 35 atom in the amine group with a group such as, for example, R-carbonyl-, RO-carbonyl-, NRR'-carbonyl- wherein R and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇) cycloalkyl, benzyl, a natural α-aminoacyl, -C(OH)C(O)OY¹ wherein Y¹ is H, (C₁-C₆)alkyl or benzyl, -C(OY²)Y³ wherein Y² is (C₁-C₄) alkyl and Y³ is (C₁-C₆)alkyl;

- 5 carboxy (C₁-C₆)alkyl; amino(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-C₆)alkylaminoalkyl; -C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N- or di-N,N-(C₁-C₆)alkylamino morpholino; piperidin-1-yl or pyrrolidin-1-yl, and the like.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the
10 hydroxy group of a hydroxyl compound, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (*e.g.*, methyl, ethyl, n-propyl, isopropyl, t-butyl, sec-butyl or n-butyl), alkoxyalkyl (*e.g.*, methoxymethyl), aralkyl (*e.g.*, benzyl), aryloxyalkyl (for example, phenoxyethyl), aryl (*e.g.*, phenyl optionally substituted with, for example, halogen,
15 C₁₋₄alkyl, -O-(C₁₋₄alkyl) or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (*e.g.*, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di (C₆₋₂₄)acyl glycerol.

20 One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves
25 varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of solvates include ethanolates, methanolates, and the like. A "hydrate" is a
30 solvate wherein the solvent molecule is water.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar
35 preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic

5 or water or mixtures thereof) at a higher than room temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The Chromane-Substituted Tetracyclic Compounds can form salts
10 which are also within the scope of this invention. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a Chromane-Substituted Tetracyclic Compound contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not
15 limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salt is a pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of the Compounds of Formula (I) may be formed, for example, by reacting a Chromane-
20 Substituted Tetracyclic Compound with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates,
25 camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from
30 basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in
35 *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and

5 magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates),
10 long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes
15 of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well-known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the
20 enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Stereochemically pure compounds may also be prepared by using chiral starting materials or by
25 employing salt resolution techniques. Also, some of the Chromane-Substituted Tetracyclic Compounds may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this invention. Enantiomers can also be directly separated using chiral chromatographic techniques.

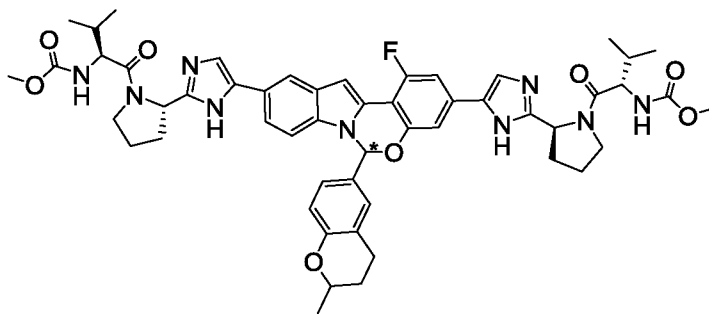
It is also possible that the Chromane-Substituted Tetracyclic
30 Compounds may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. For example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates,
35 esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are

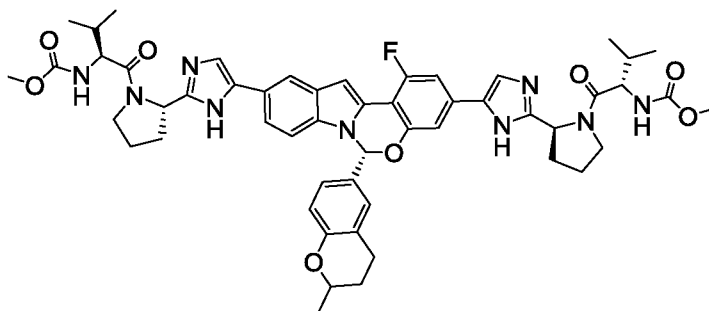
5 contemplated within the scope of this invention. If a Chromane-Substituted Tetracyclic Compound incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as
 10 racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the
 15 inventive compounds.

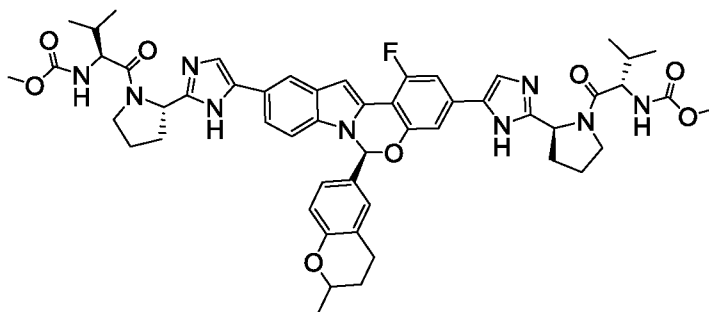
When a substituent on a chiral carbon atom is depicted as a racemate (by using a straight line bond to a chiral center), it is to be understood that both the alpha and beta configurations of said substituent group are to be considered part of the present invention. For example, the compound of the present invention, which is
 20 drawn as follows:



is understood to encompass both diastereomers at the indicated chiral center, the structures of which are as follows:



and



5

In the Examples section below, compounds of the present invention that have been purified into pure diastereomers are sometimes depicted in racemic form but identified as “Isomer 1” and “Isomer 2.” In this instance, the absolute stereochemistry of each isolated diastereomer has not been determined and the Isomer 1 and Isomer 2 designations are used to represent each individual purified diastereomer.

In the Compounds of Formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched Compounds of Formula (I) can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates. In one embodiment, a Compound of Formula (I) has one or more of its hydrogen atoms replaced with deuterium.

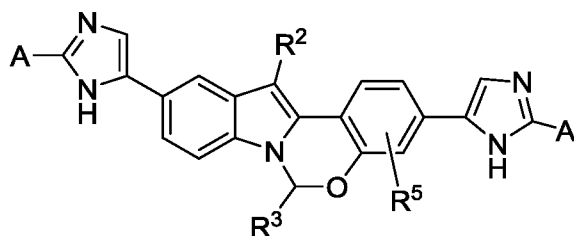
Polymorphic forms of the Chromane-Substituted Tetracyclic Compounds, and of the salts, solvates, hydrates, esters and prodrugs of the Chromane-Substituted Tetracyclic Compounds, are intended to be included in the present invention.

The following abbreviations are used below and have the following meanings: Ac is acyl; Aq is aqueous; $\text{BF}_3\cdot\text{OEt}$ is boron trifluoride etherate; BOC or

- 5 Boc is *tert*-butoxycarbonyl; Boc₂O is Boc anhydride; n-BuPACl₂ is adamantyl n-butylphosphine dichloride; t-Bu is tertiary butyl; t-BuOK is potassium *tert*-butoxide; n-BuLi is n-butyllithium; Celite is the tradename for diatomaceous earth; conc. is concentrated; Cp₂TiCl₂ is di(cyclopentadienyl)titanium(IV) dichloride; DAST is diethylaminosulfur trifluoride; DCM is dichloromethane; DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Deoxofluor is bis(2-methoxyethyl)aminosulfur trifluoride; DIAD is diisopropylazodicarboxylate; DIBAL is diisobutylaluminum hydride; DIPEA is diisopropylethylamine; DMA is dimethylacetamide; DME is dimethoxyethane; DMF is *N,N*-dimethylformamide; dppf is diphenylphosphinoferrocene; DMSO is dimethylsulfoxide; ESI is electrospray ionization; EtOAc is ethyl acetate; EtOH is ethanol; HATU is O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HPLC is high performance liquid chromatography; KOAc is potassium acetate; LCMS is liquid chromatography/mass spectrometry; LiHMDS is lithium hexamethyldisilazide; MeCN is acetonitrile; Me is methyl; MeLi is methyllithium; MeOH is methanol; MS is mass spectrometry; Na₂EDTA is disodium ethylenediaminetetraacetate; NMP is *N*-methylpyrrolidinone; PCR is polymerase chain reaction; Pd₂(dba)₃ is tris(dibenzylideneacetone)dipalladium(0); Pd(dppf)₂Cl₂ is [1,1'-Bis(diphenylphosphino)ferrocene] dichloro palladium(II); Ph is phenyl; PIFA is phenyliodine bis(trifluoroacetate); RT-PCR is reverse transcription polymerase chain reaction; SFC is supercritical flow chromatography; TFA is trifluoroacetic acid; THF is tetrahydrofuran; TLC is thin-layer chromatography; TsOH is *p*-toluenesulfonic acid; XPhos is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; and ZnEt₂ is diethyl zinc.

30 The Compounds of Formula (I)

The present invention provides Chromane-Substituted Tetracyclic Compounds of Formula (I):



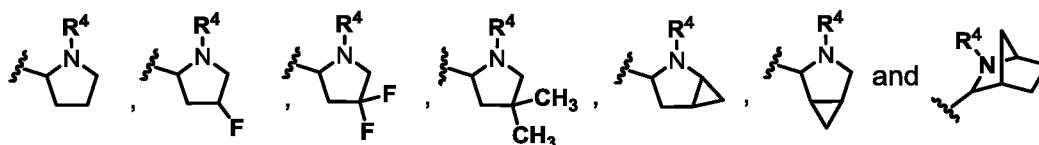
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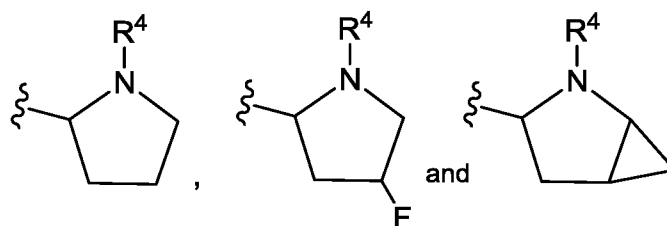
and pharmaceutically acceptable salts thereof, wherein A, A', R², R³ and R⁵ are defined above for the Compounds of Formula (I).

10 In one embodiment, for the compounds of formula (I), A and A' are each a 5-membered heterocycloalkyl group.

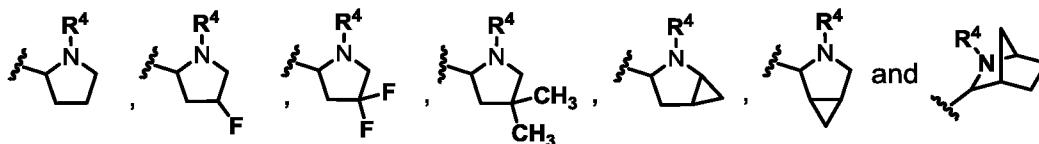
In another embodiment, for the compounds of formula (I), A and A' are each independently selected from:



15 In another embodiment, for the compounds of formula (I), A and A' are each independently selected from:

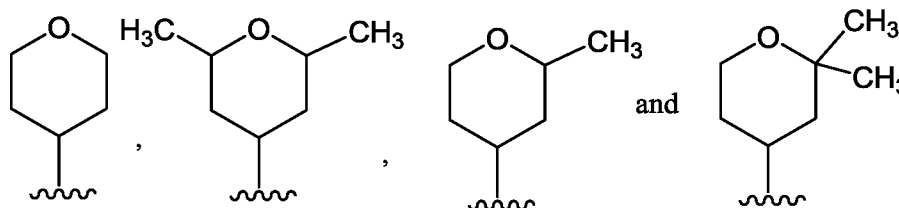


In one embodiment, for the compounds of formula (I), A and A' are each independently selected from:



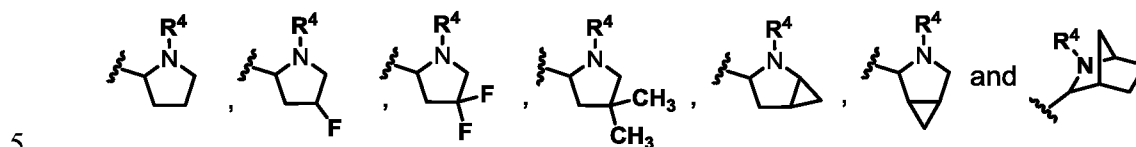
20

and each occurrence of R⁴ is independently -C(O)CH(R⁷)NHC(O)OCH₃, wherein R⁷ is selected from: isopropyl, -CF(CH₃)₂,

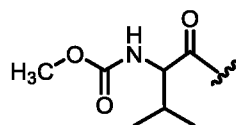


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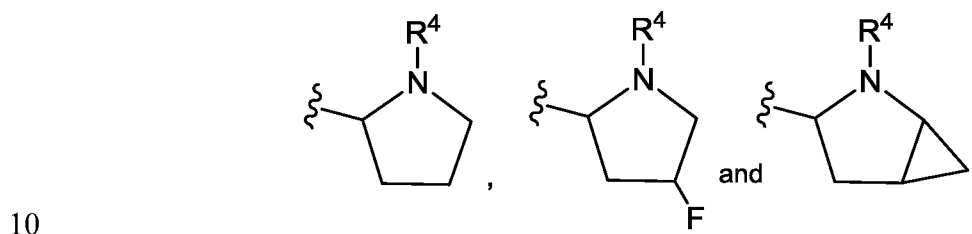
In another embodiment, for the compounds of formula (I), A and A' are each independently selected from:



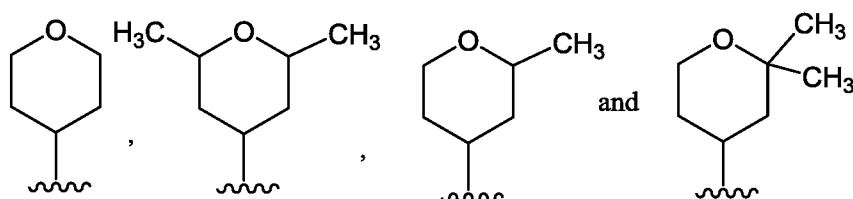
and each occurrence of R^4 is:



In another embodiment, for the compounds of formula (I), A and A' are each independently selected from:



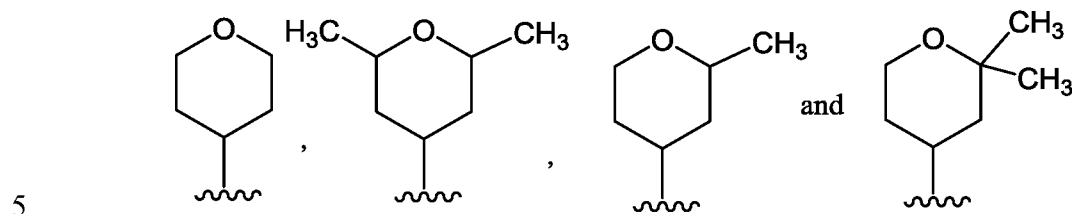
each occurrence of R^4 is independently $-C(O)CH(R^7)NHC(O)OCH_3$, wherein R^7 is selected from: isopropyl, $-CF(CH_3)_2$, $-CH(CH_3)OCH_2CH_3$,



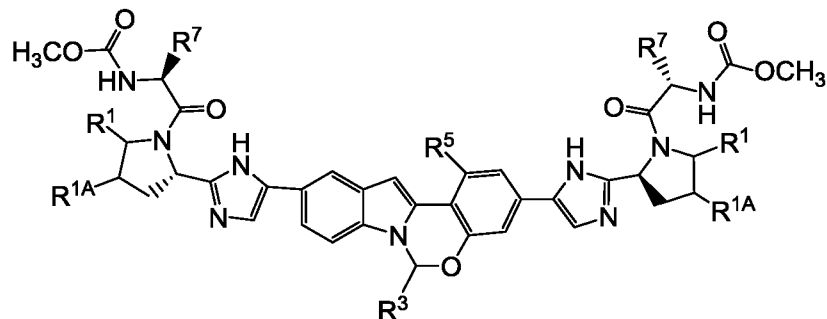
15 In one embodiment, for the compounds of formula (I), each occurrence of R^4 is independently $-C(O)CH(R^7)NHC(O)OCH_3$.

In another embodiment, for the compounds of formula (I), each occurrence of R^4 is independently $-C(O)CH(R^7)NHC(O)OCH_3$, and each occurrence of R^7 is independently selected from C_1 - C_6 alkyl, C_1 - C_6 haloalkyl and 4 to 6-membered monocyclic heterocycloalkyl, wherein said 4 to 6-membered monocyclic heterocycloalkyl group can be optionally substituted with up to five C_1 - C_6 alkyl groups or said 4 to 6-membered monocyclic heterocycloalkyl group can be optionally substituted on a ring carbon atom with a spirocyclic C_3 - C_6 cycloalkyl group.

25 In one embodiment, for the compounds of formula (I), each occurrence of R^4 is independently $-C(O)CH(R^7)NHC(O)OCH_3$, wherein R^7 is selected from: isopropyl, $-CF(CH_3)_2$, $-CH(CH_3)OCH_2CH_3$,



In one embodiment, the compound of formula (I) has the formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof,

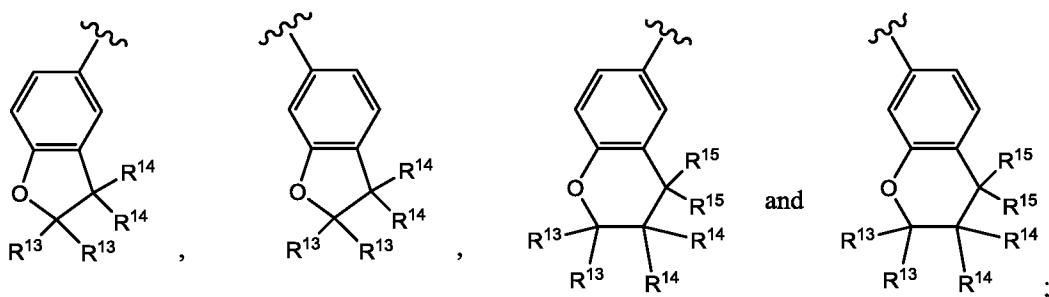
wherein:

each R^1 is H;

each R^{1A} is independently H or F, or an R^{1A} group and an R^1 group that

are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused cyclopropyl group;

R^3 is selected from:



R^5 is H, F or methyl;

each occurrence of R^7 is independently selected from C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, phenyl and 4 to 6-membered monocyclic heterocycloalkyl, wherein said 4 to 6-membered monocyclic heterocycloalkyl group can be optionally substituted with up to 2 groups, each independently selected from C_1 - C_6 alkyl;

5 each occurrence of R^{13} is independently selected from H and C_1-C_6 alkyl, or both R^{13} groups and the common carbon atom to which they are each attached, join to form a spirocyclic C_3-C_7 cycloalkyl group;

each occurrence of R^{14} is independently selected from H, halo and C_1-C_6 alkyl; or both R^{14} groups and the common carbon atom to which they are each attached, join to form a spirocyclic C_3-C_7 cycloalkyl group; or an R^{14} group and R^{13} group, together with the carbon atoms to which they are each attached, join to form a fused C_3-C_7 cycloalkyl group; or an R^{14} group and R^{15} group, together with the carbon atoms to which they are each attached, join to form a fused C_3-C_7 cycloalkyl group; and

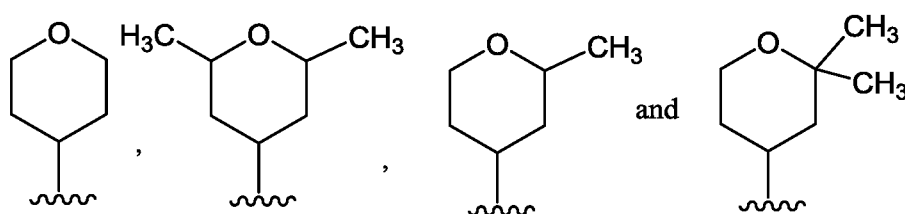
15 each occurrence of R^{15} is independently selected from H, C_1-C_6 alkyl and halo, or both R^{15} groups and the common carbon atom to which they are each attached, join to form a spirocyclic C_3-C_7 cycloalkyl group.

In one embodiment, for compounds of formula (Ia), each occurrence of R^1 is H.

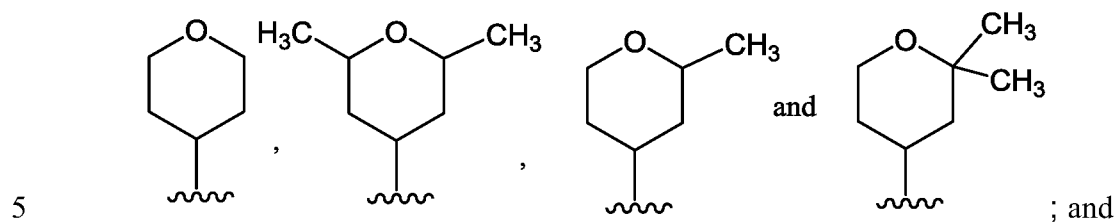
20 In one embodiment, for compounds of formula (Ia), each occurrence of R^{1A} is independently H or F.

In another embodiment, for compounds of formula (Ia), one or both R^1 groups combine with the adjacent R^{1A} group to form a fused cyclopropyl group.

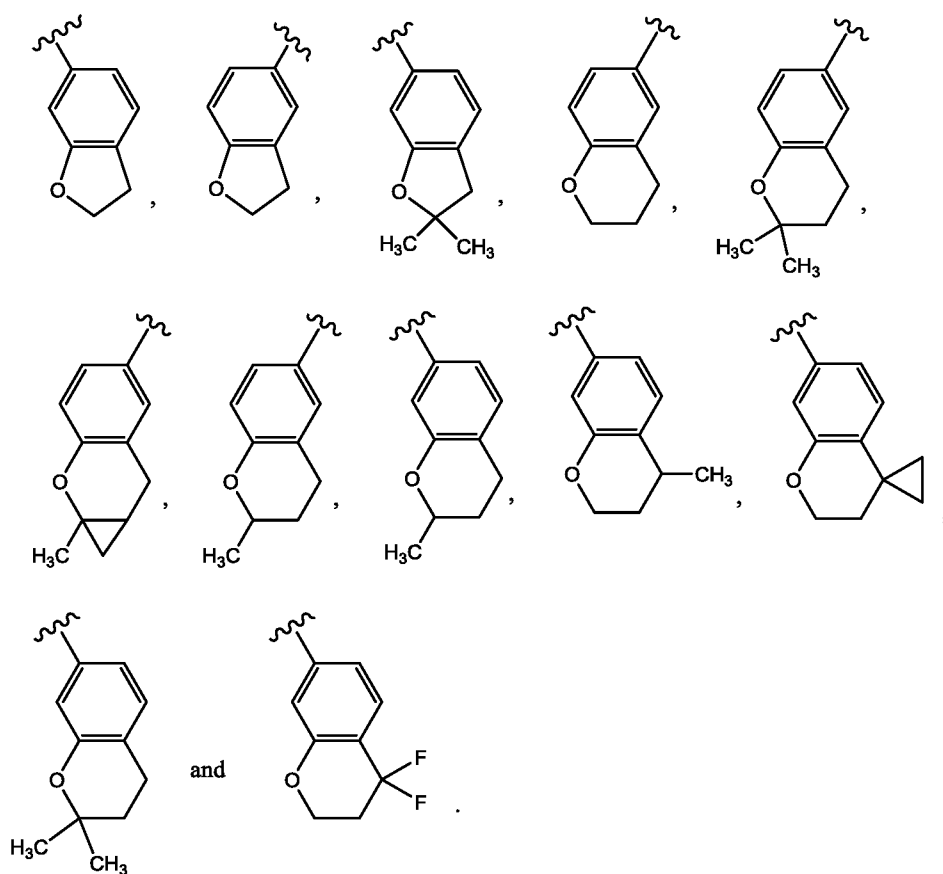
25 In one embodiment, for compounds of formula (Ia), each occurrence of R^7 is independently selected from: isopropyl, $-CF(CH_3)_2$, $-CH(CH_3)OCH_2CH_3$,



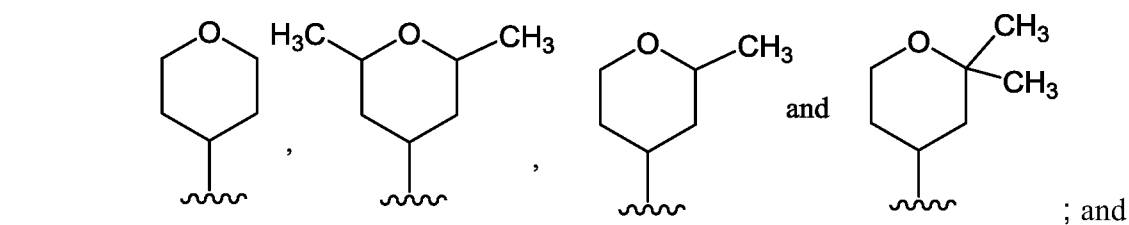
30 In another embodiment, for the compounds of formula (Ia), each occurrence of R^7 is independently selected from: isopropyl, $-CF(CH_3)_2$, $-CH(CH_3)OCH_2CH_3$,



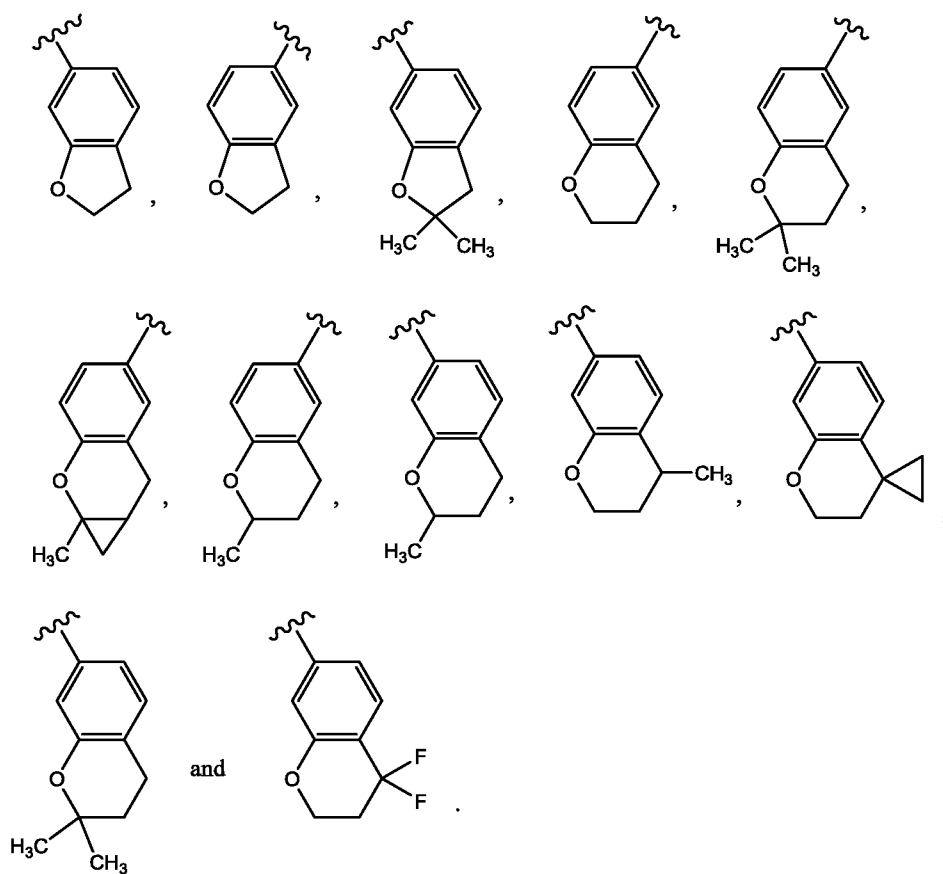
R^3 is selected from:



10 In another embodiment, for the compounds of formula (Ia), R^5 is H, F or methyl; each occurrence of R^7 is independently selected from: isopropyl, - $CF(CH_3)_2$, - $CH(CH_3)OCH_2CH_3$,



R^3 is selected from:



5

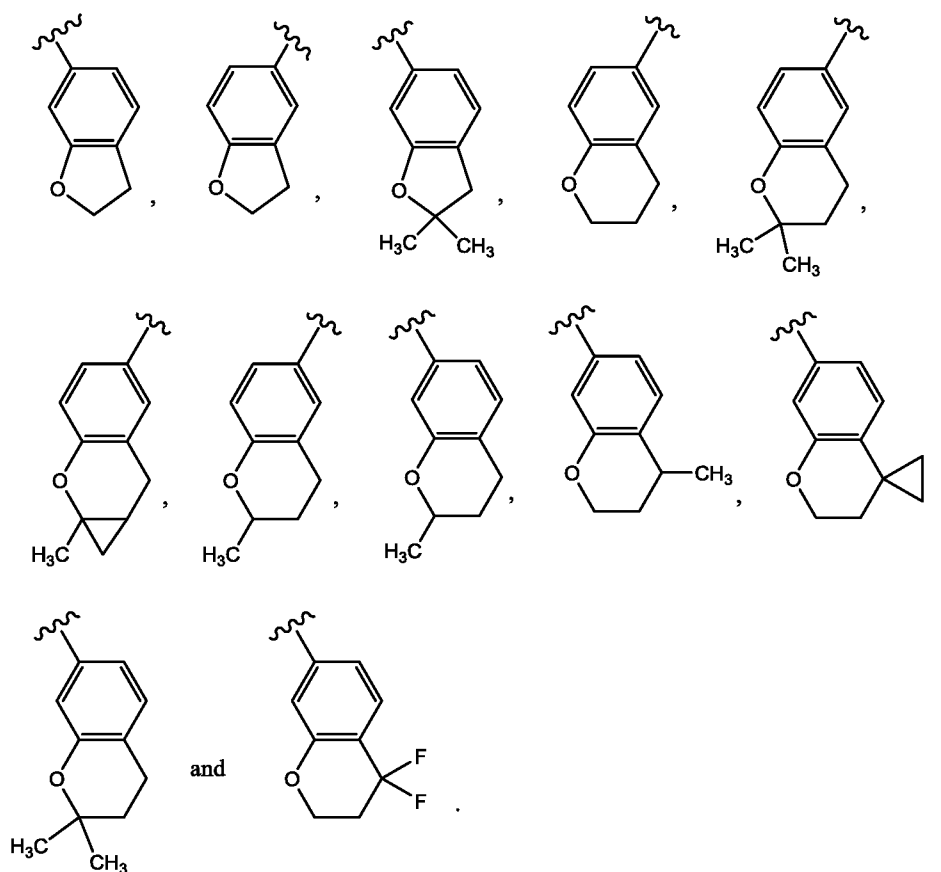
In one embodiment, for the compounds of formula (I) or (Ia), R^2 is H

In another embodiment, for the compounds of formula (I) or (Ia), R^2 is halo.

10

In another embodiment, for the compounds of formula (I) or (Ia), R^2 is C_1 - C_6 alkyl.

In one embodiment, for the compounds of formula (I) or (Ia), R^3 is selected from:



5

In one embodiment, for the compounds of formula (I) or (Ia), R^5 is absent.

In another embodiment, for the compounds of formula (I) or (Ia), R^5 is

10 F.

In another embodiment, for the compounds of formula (I) or (Ia), R^5 is C_1 - C_6 alkyl.

In still another embodiment, for the compounds of formula (I) or (Ia), R^5 is methyl.

15 In one embodiment, variables A, A', R^2 , R^3 and R^5 for the Compounds of Formula (I) are selected independently of each other.

In another embodiment, the Compounds of Formula (I) are in substantially purified form.

20 In one embodiment, variables R^1 , R^{1A} , R^3 , R^5 and R^7 for the Compounds of Formula (Ia) are selected independently of each other.

In another embodiment, the Compounds of Formula (Ia) are in substantially purified form.

Other embodiments of the present invention include the following:

5 (a) A pharmaceutical composition comprising an effective amount of a Compound of Formula (I), and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

10 (c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(d) A pharmaceutical combination that is (i) a Compound of Formula (I) and (ii) a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents; wherein the Compound of Formula (I) and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV replication, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

20 (e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(f) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

25 (g) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

30 (h) The method of (g), wherein the Compound of Formula (I) is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

5 (j) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

(k) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof
10 which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

Additional embodiments of the present invention include the following:

(l) A pharmaceutical composition comprising an effective amount
15 of a pharmaceutically acceptable salt of a Compound of Formula (I), and a pharmaceutically acceptable carrier.

(m) The pharmaceutical composition of (l), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

20 (n) The pharmaceutical composition of (m), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(o) A pharmaceutical combination that is (i) a pharmaceutically acceptable salt of a Compound of Formula (I) and (ii) a second therapeutic agent
25 selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents; wherein the pharmaceutically acceptable salt of the Compound of Formula (I) and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV replication, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

30 (p) The combination of (o), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(q) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject an effective amount of a
35 pharmaceutically acceptable salt of a Compound of Formula (I).

(r) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof

5 which comprises administering to the subject an effective amount of a pharmaceutically acceptable salt of a Compound of Formula (I).

(s) The method of (r), wherein the pharmaceutically acceptable salt of the Compound of Formula (I) is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of
10 HCV antiviral agents, immunomodulators, and anti-infective agents.

(t) The method of (s), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(u) A method of inhibiting HCV replication in a subject in need
15 thereof which comprises administering to the subject the pharmaceutical composition of (l), (m) or (n) or the combination of (o) or (p).

(v) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (l),
20 (m) or (n) or the combination of (o) or (p).

Further embodiments of the present invention include the following:

(w) A pharmaceutical composition comprising an effective amount of a Compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25 (x) The pharmaceutical composition of (w), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(y) The pharmaceutical composition of (x), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease
30 inhibitors and HCV NS5B polymerase inhibitors.

(z) A pharmaceutical combination that is (i) a Compound of Formula (I) and (ii) or a pharmaceutically acceptable salt thereof, a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents; wherein the Compound of Formula (I) and the second
35 therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV replication, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

5 (aa) The combination of (z), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(bb) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject an effective amount of a
10 Compound of Formula (I) or a pharmaceutically acceptable salt thereof.

(cc) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I) or a pharmaceutically acceptable salt thereof.

15 (dd) The method of (cc), wherein the Compound of Formula (I) or pharmaceutically acceptable salt thereof, is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(ee) The method of (dd), wherein the HCV antiviral agent is an
20 antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(ff) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (w) (x) or (y) or the combination of (z) or (aa).

25 (gg) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (w) (x) or (y) or the combination of (z) or (aa).

The present invention also includes a compound of the present
30 invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) medicine; (b) inhibiting HCV replication or (c) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral
35 agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention

- 5 employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

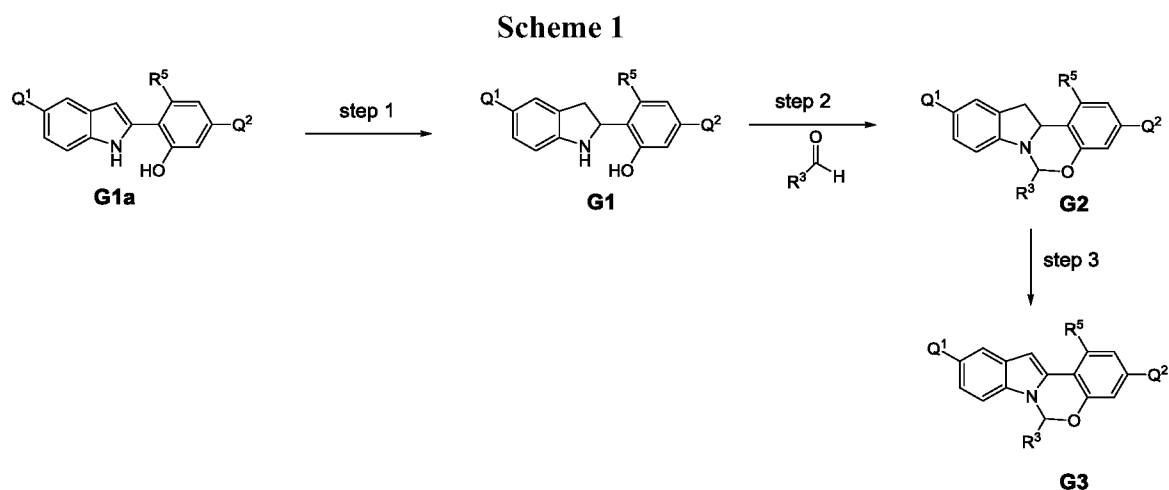
- 10 It is further to be understood that the embodiments of compositions and methods provided as (a) through (k) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

- 15 Non-limiting examples of the Compounds of Formula (I) include compounds **1-94**, as set forth in the Examples below, and pharmaceutically acceptable salts thereof.

Methods For Making the Compounds of Formula (I)

- 20 The Compounds of Formula (I) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in Schemes 1-4 below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art
- 25 of organic synthesis.

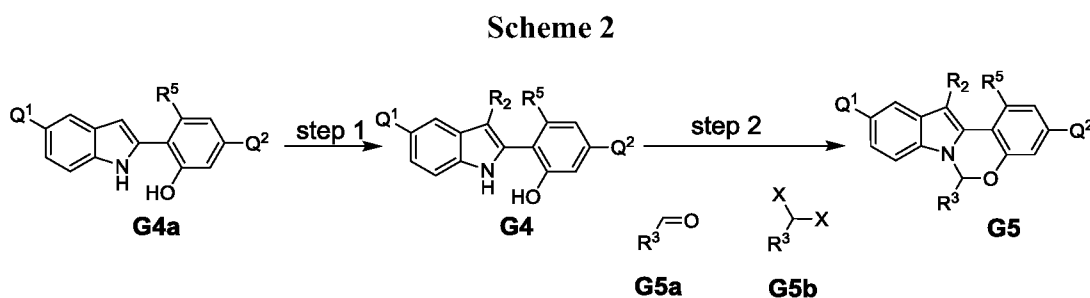
Scheme 1 shows methods useful for making the compounds of formula **G3**, which are useful intermediates for making the Compounds of Formula (I).



- 5 Wherein R^3 and R^5 are defined above for the Compounds of Formula (I) and Q^1 and Q^2 are each independently halo, hydroxyl, or a protected hydroxyl group, such as a methoxy or benzyloxy group.

 An indole compound of formula **G1a** (which can be prepared as described in International Publication No. WO 2012/040923) can be treated with tin
 10 in concentrated HCl/EtOH solution to provide compounds of formula **G1**. A compound of formula **G1** can be reacted with an aldehyde of formula $R^3\text{CHO}$ in the presence of an acid to provide tetracyclic compounds of formula **G2**. Compounds of formula **G2** can then be oxidized to provide the tetracyclic compounds of formula **G3**.

 Scheme 2 shows methods useful for making the compounds of formula
 15 **G5**, which are useful intermediates for making the Compounds of Formula (I).



- Wherein R^2 is halo, R^3 and R^5 are defined above for the Compounds of
 20 Formula (I), X is halo, and Q^1 and Q^2 are each independently halo, hydroxyl, or a protected hydroxyl group, such as a methoxy or benzyloxy group.

 A compound of formula **G4a** (which can be prepared as described in International Publication No. WO 2012/040923) can be halogenated to provide the compounds of formula **G4**, wherein R^2 is halo. A compound of formula **G4** can then
 25 be converted to the compounds of formula **G5** via reaction with an aldehyde of formula **G5a** in the presence of an acid, or alternatively, by reaction with a dihalo compound of formula **G5b** in the presence of a base. The R^2 group of the compounds of formula **G5** can be further elaborated using methods well-known in the art of organic synthesis to make the entire scope of variable R^2 .

30 Scheme 3 shows methods useful for making the compounds of formula **G12**, which are useful intermediates for making the Compounds of Formula (I).

Scheme 3



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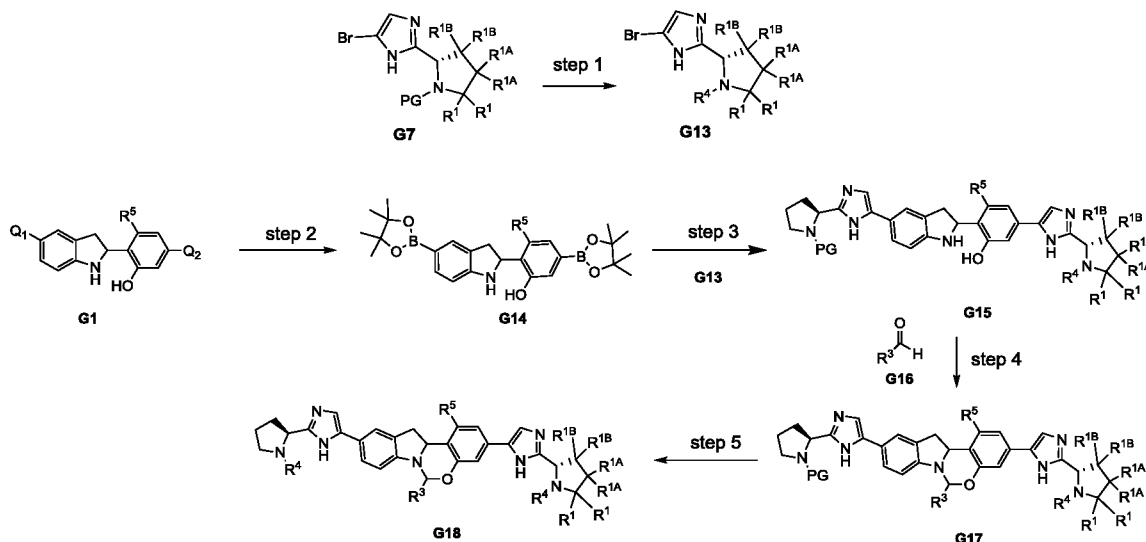
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5 Scheme 4 shows methods useful for making the compounds of formula **G18**, which correspond to the Compounds of Formula (I).

Scheme 4



10 Wherein R^3 , R^4 and R^5 are defined above for the Compounds of Formula (I), PG is a secondary amino protecting group, and Q^1 and Q^2 are each independently halo, hydroxyl, or a protected hydroxyl group, such as a methoxy or benzyloxy group.

A compound of formula **G7** can be deprotected and subjected to an
 15 amide coupling with a desired cap compound to provide an intermediate bromoimidazole compound of formula **G13**. A compound of formula **G1** can be converted to compound of formula **G14** via a Pd-mediated coupling reaction with bis(pinacolato)diboron. The compound of formula **G14** can then be subjected to a Pd-mediated coupling with a compound of formula **G13** to provide a compound of
 20 formula **G15**. The compound of formula **G15** can then be converted a compound of formula **G17** via reaction with an aldehyde of formula **G16** in the presence of an acid. The compound of formula **G17** can then be subjected to an oxidative cyclization to provide the tetracyclic compounds of formula **G18**. The distereoisomers of **G18** can be separated using, for example, SFC and employing chiral columns.

25 One skilled in the art of organic synthesis will recognize that the synthesis of fused tetracyclic cores contained in Compounds of Formula (I) may require protection of certain functional groups (*i.e.*, derivatization for the purpose of chemical compatibility with a particular reaction condition). Suitable protecting groups for the various functional groups of these Compounds and methods for their

5 installation and removal are well known in the art of organic chemistry. A summary of many of these methods can be found in Greene *et al.*, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

One skilled in the art of organic synthesis will also recognize that one route for the synthesis of the fused tetracyclic cores of the Compounds of Formula (I)
10 may be more desirable depending on the choice of appendage substituents. Additionally, one skilled in the art will recognize that in some cases the order of reactions may differ from that presented herein to avoid functional group incompatibilities and thus adjust the synthetic route accordingly.

The preparation of multicyclic intermediates useful for making the fused tetracyclic ring systems of the Compounds of Formula (I) have been described in the literature and in compendia such as "Comprehensive Heterocyclic Chemistry" editions I, II and III, published by Elsevier and edited by A.R. Katritzky & R. JK Taylor. Manipulation of the required substitution patterns have also been described in the available chemical literature as summarized in compendia such as
15 "Comprehensive Organic Chemistry" published by Elsevier and edited by DH R. Barton and W. D. Ollis; "Comprehensive Organic Functional Group Transformations" edited by edited by A.R. Katritzky & R. JK Taylor and "Comprehensive Organic Transformation" published by Wiley-CVH and edited by R. C. Larock.

The starting materials used and the intermediates prepared using the methods set forth in Schemes 1-4 may be isolated and purified if desired using
25 conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and alike. Such materials can be characterized using conventional means, including physical constants and spectral data.

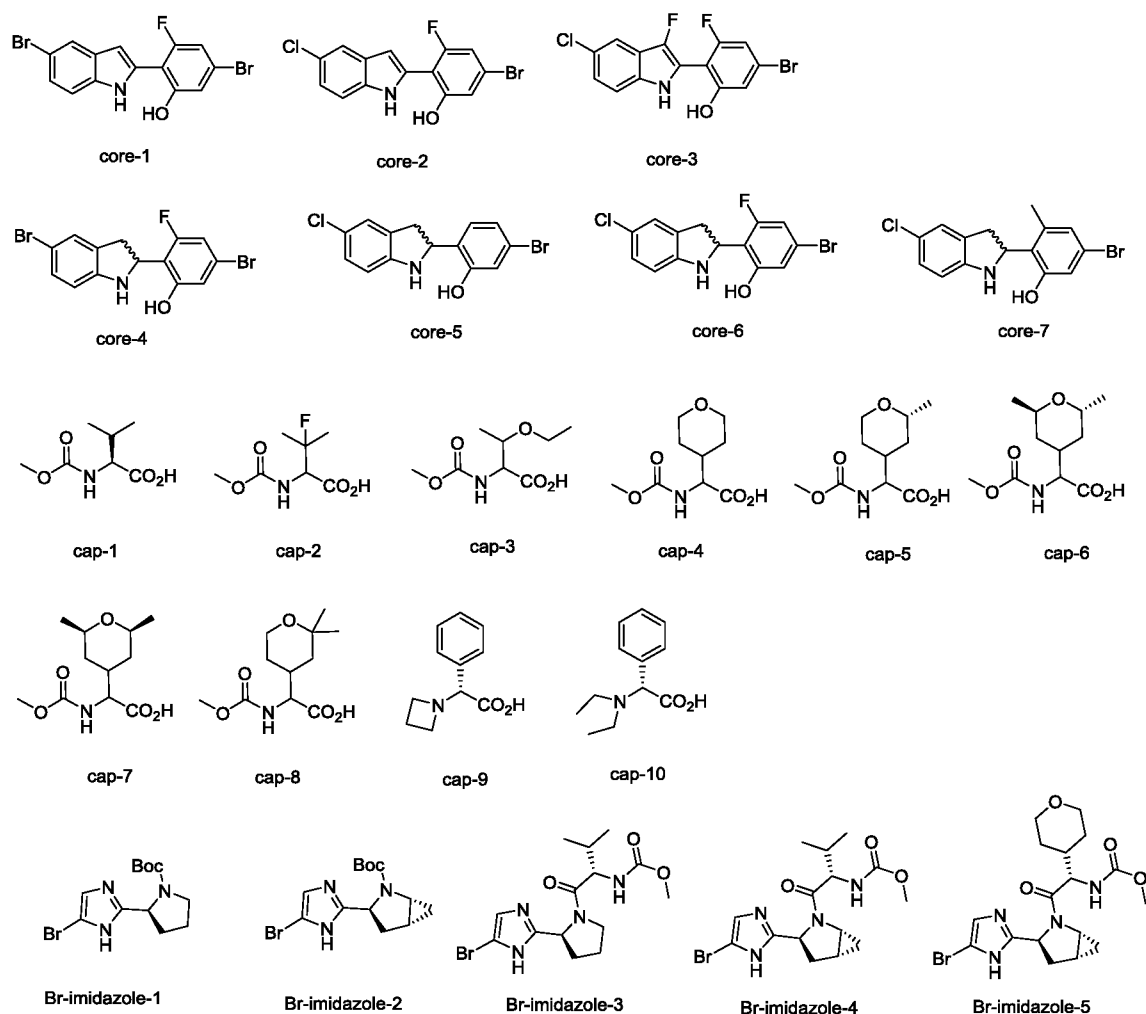
30 EXAMPLES

General Methods

Solvents, reagents, and intermediates that are commercially available were used as received. Reagents and intermediates that are not commercially available were prepared in the manner as described below. ¹H NMR spectra were
35 obtained on a Bruker Avance 500 (500 MHz) and are reported as ppm downfield from Me₄Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed

- 5 using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33 mm x 7mm ID; gradient flow: 0 minutes – 10% CH₃CN, 5 minutes – 95% CH₃CN, 5-7 minutes – 95% CH₃CN, 7 minutes – stop. The retention time and observed parent ion are given. Flash column chromatography was performed using pre-packed normal phase silica from Biotage, Inc. or bulk silica from Fisher Scientific. Unless otherwise indicated, column chromatography was performed using a gradient elution of hexanes/ethyl acetate, from 100% hexanes to 100% ethyl acetate.

- 15 The following intermediates, which are useful for making the compounds of the present invention, can be made using methods described in International Patent Publication Nos. WO2014110705 and WO2014110706.

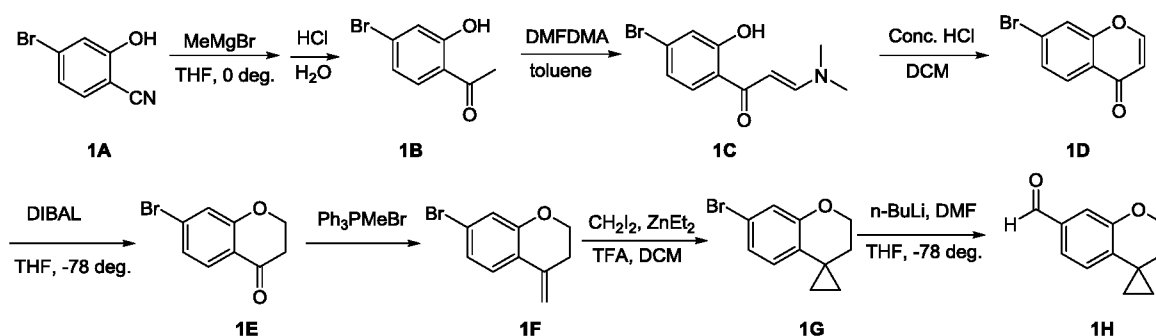


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Example 1

Preparation of Intermediate Compound 1H

5



Step 1

To a solution of compound **1A** (48 g, 244 mmol) in THF (1500 mL) was added MeMgBr (3 M in diethyl ether, 450 mL, 1350 mmol) dropwise under nitrogen at -40°C for 30 minutes. The mixture was allowed to stir at -40°C for 1 hour, then at room temperature for 16 hours. Water (1000 mL) and conc. HCl (200 mL) were added and stirred at room temperature for 24 hours, then extracted with ethyl acetate. The organic extract was washed with saturated NaHCO₃, brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide compound **1B** as a solid.

¹H-NMR (CDCl₃, 400 MHz): δ 12.32 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.15 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 2.59 (s, 3H).

Step 2

To a solution of compound **1B** (48 g, 224 mmol) in dry toluene (500 mL) was added N, N-dimethylformamide (53.3 g, 448 mmol) at room temperature. The mixture was heated to reflux and allowed to stir at this temperature for 16 hours, then cooled, and filtered. The collected solid was washed with toluene to provide compound **1C** as a solid. The filtrate was concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 5: 1) to provide additional amount of compound **1C** as a solid.

¹H-NMR (CDCl₃, 400 MHz): δ 7.85 (d, *J* = 12.0 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.26 (s, 1H), 7.09 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 5.66 (d, *J* = 12.0 Hz, 1H), 3.18 (s, 3H), 2.95 (s, 3H).

Step 3

5 To a solution of compound **1C** (37 g, 137.5 mmol) in dichloromethane (400 mL) was added conc. HCl (115 mL, 1.375 mole) at room temperature. The mixture was stirred at reflux for 2 hours, and extracted with dichloromethane. The organic extract was washed with saturated NaHCO₃, brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide compound **1D** as a solid, which was
10 used without further purification. ¹H-NMR (CDCl₃, 400 MHz): δ 8.04 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 6.4 Hz, 1H), 7.63 (s, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 6.32 (d, *J* = 6.4 Hz, 1H).

Step 4

15 To a solution of compound **1D** (32.6 g, 145.5 mmol) in THF (600 mL) was added DIBAL (1 M in toluene, 437 mL, 437 mmol) dropwise under nitrogen at -78°C for 30 minutes. The mixture was allowed to stir at -78°C for 1 hour, then the reaction mixture was poured into 500 mL of 1 M aq. HCl, and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate,
20 filtered and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 20: 1 to provide compound **1E** as a solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.13-7.17 (m, 2H), 4.52 (t, *J* = 6.4 Hz, 1H), 2.79 (d, *J* = 6.4 Hz, 1H).

25 *Step 5*

To a solution of methyltriphenylphosphonium bromide (40.45 g, 111.31 mmol) in THF (500 mL) was added n-BuLi (2.5 M in hexane, 45.3 mL, 111.31 mmol) dropwise at 0°C under nitrogen. The resulting reaction was allowed to stir at 0°C for 1 hours and then a solution of compound **1E** (21.34 g, 94.62 mmol) in
30 THF (100 mL) was added. The mixture was allowed to stir at 0°C for 1 hour, then at room temperature for another 1 hour. The reaction was quenched by addition of aq. NH₄Cl, and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl
35 acetate = 50: 1 to provide compound **1F** as an oil. ¹H-NMR (CDCl₃, 400 MHz): δ 7.38 (d, *J* = 8.8 Hz, 1H), 6.97-6.99 (m, 2H), 5.47 (s, 1H), 4.89 (s, 1H), 4.20 (t, *J* = 5.6 Hz, 2H), 2.64 (t, *J* = 5.6 Hz, 2H).

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Step 6

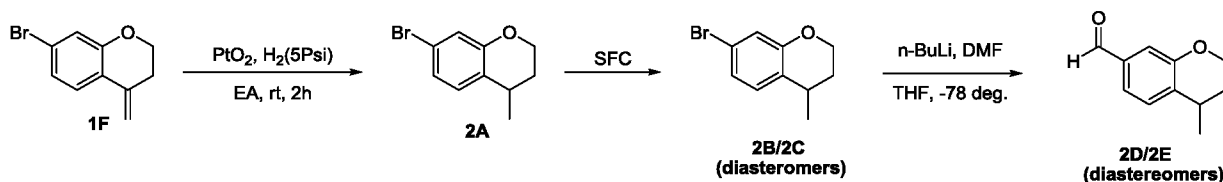
CH₂I₂ (17.17 g, 66 mmol) was added dropwise to a stirred solution of ZnEt₂ (1 M in hexane, 33 mL, 33 mmol) in dichloromethane (33 mL) at -78°C under nitrogen, and the mixture was allowed to stir at 0°C for 15 minutes resulting in the formation of a precipitate. TFA (3.77 mL, 33 mmol) was added to the mixture resulting in the rapid formation of a homogeneous solution which was allowed to stir at 0°C for 15 minutes. A solution of compound **1F** (3.7 g, 16.5 mmol) in dichloromethane (10 mL) was then added and the resulting reaction was allowed to stir at room temperature for 16 hours. Saturated Na₂EDTA (70 mL) was then added and the resulting reaction was vigorously stirred for 5 minutes, then diluted with dichloromethane (100 mL) and saturated NaHCO₃ (100 mL). The aqueous layer was extracted with dichloromethane, and the organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 50: 1) to provide compound **1G** as a solid. ¹H-NMR (CDCl₃, 400 MHz): δ 6.89-6.94 (m, 2H), 6.47 (d, *J* = 8.4 Hz, 1H), 4.25 (t, *J* = 5.2 Hz, 2H), 1.82 (t, *J* = 5.2 Hz, 2H), 1.00 (t, *J* = 5.2 Hz, 2H), 0.82 (t, *J* = 5.2 Hz, 2H).

Step 7

To a solution of compound **1G** (0.77 g, 3.24 mmol) in THF (13 mL) was added n-BuLi (2.5 M in hexane, 2 mL, 5 mmol) dropwise at -78°C under nitrogen. The mixture was allowed to stir at -78°C for 5 minutes. The reaction was diluted with DMF (1 mL, 13 mmol), then allowed to stir at -78°C for an additional 1 hour. The reaction was quenched by addition aq. NH₄Cl, and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue obtained was purified using pre-TLC (petroleum ether: ethyl acetate = 20: 1) to provide compound **1H** as an oil. MS (ESI) *m/z*: 189.0 [M+H]⁺.

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Example 2Preparation of Intermediate Compound **2D** and **2E**



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Step 1

A solution of compound **1F** (3.2 g, 14.3 mmol) and PtO_2 (3.2 g) in ethyl acetate (50 mL) was allowed to stir under hydrogen balloon at room temperature for 2 hours, then the reaction mixture was filtered and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 100: 1) to provide compound **2A** as an oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 6.93-6.99 (m, 3H), 4.10-4.20 (m, 2H), 2.83-2.91 (m, 1H), 2.00-2.08 (m, 1H), 1.67-1.72 (m, 1H), 1.65-1.66 (m, 3H).

15

Step 2

Compound **2A** was separated using SFC to provide two diastereomers **2B** and **2C**. Column: Chiralpak AS-H 250×20 mm I.D., 5 μm Mobile phase: 40% of IPA/ NH_4OH in CO_2 , Flow rate: 50 mL/min, Wavelength: 340 nm. The stereochemistry of **2B** and **2C** were assigned arbitrarily.

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Step 3

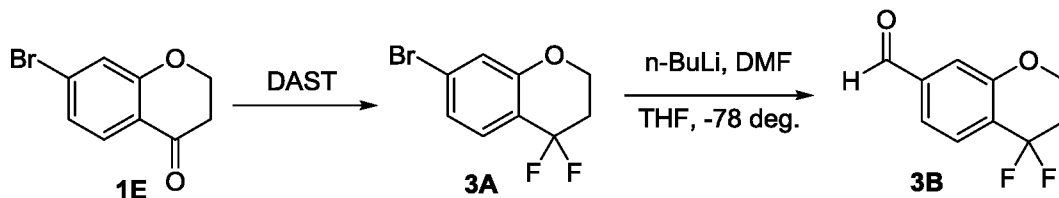
To a solution of compound **2B** (1 g, 4.42 mmol) in THF (10 mL) was added $n\text{-BuLi}$ (2.5 M in hexane, 5.3 mL, 13.27 mmol) dropwise at -78°C under nitrogen. The mixture was allowed to stir at -78°C for 10 minutes, then DMF (2 mL, 26.55 mmol) was added and the resulting reaction was allowed to stir at -78°C for 1 hour. The reaction was quenched by addition aq. NH_4Cl , and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide compound **2D** as an oil, which was used without further purification.

30

Compound **2E** was prepared from compound **2C** using the methodology described in Step 3 immediately above.

35

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Example 3Preparation of Intermediate Compound **3B***Step 1*

10 Deoxofluor (10 mL, 50 mmol) was added to a solution of compound **1E** (1.13 g, 5 mmol) in DCM (2 mL) and EtOH (0.1 mL) in a sealed tube. The reaction was heated to 40°C and allowed to stir at this temperature for 24 hours. The reaction mixture was then poured into ice-water and basified to pH 9 using aqueous Na_2CO_3 . The basified solution was extracted with DCM, and the organic extract was

15 washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel eluted with petroleum ether to provide compound **3A** as an oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.42 (d, $J = 8.4$ Hz, 1H), 7.11 (d, $J = 8.8$ Hz, 1H), 7.06 (s, 1H), 4.34 (t, $J = 5.6$ Hz, 2H), 2.39-2.49 (m, 2H).

20

Step 2

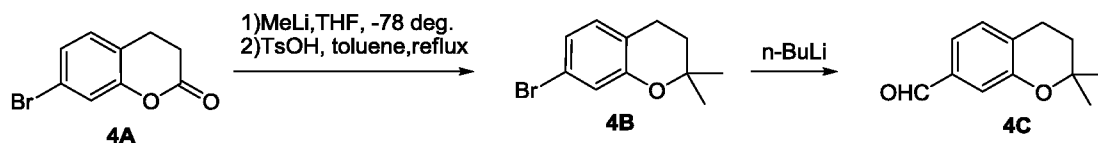
To a solution of compound **3A** (0.7 g, 2.8 mmol) in THF (10 mL) at -78°C was added $n\text{-BuLi}$ (2.5 M in hexane, 3.5 mL, 8.75 mmol) dropwise under nitrogen. The reaction was allowed to stir at -78°C for 5 minutes, then DMF (1.4 mL,

25 18.2 mmol) was added. The resultant mixture was allowed to stir at -78°C for 1 hour, then the reaction was quenched by addition aq. NH_4Cl , and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 20: 1) to

30 provide compound **3B** as an oil. $^1\text{H-NMR}$ (CDCl_3 400 MHz): δ 9.96 (s, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.37 (s, 1H), 4.40 (t, $J = 6.0$ Hz, 2H), 2.45-2.54 (m, 2H).

Example 4

5

Preparation of Intermediate Compound **4C***Step 1*

10 To a solution of compound **4A** (2.26 g, 10 mmol) in THF (30 mL) at 0 °C was added MeLi (1.6 M in ether, 15.6 mL, 25 mmol) dropwise under nitrogen. The mixture was allowed to stir at room temperature for 3 hours, then re-cooled to 0 °C using an ice bath, and aq. 1M HCl (2.5 mL) was added dropwise. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The organic extract

15 was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue obtained was dissolved in toluene (30 mL), TsOH-H₂O (95 mg, 0.5 mmol) was added, and the mixture was stirred at reflux for 16 hours in a Dean-Stark apparatus. The reaction mixture was then concentrated in vacuo, and the resulting residue obtained was purified using flash column chromatography on silica gel

20 (petroleum ether: ethyl acetate = 300: 1 to provide compound **4B** as an oil.

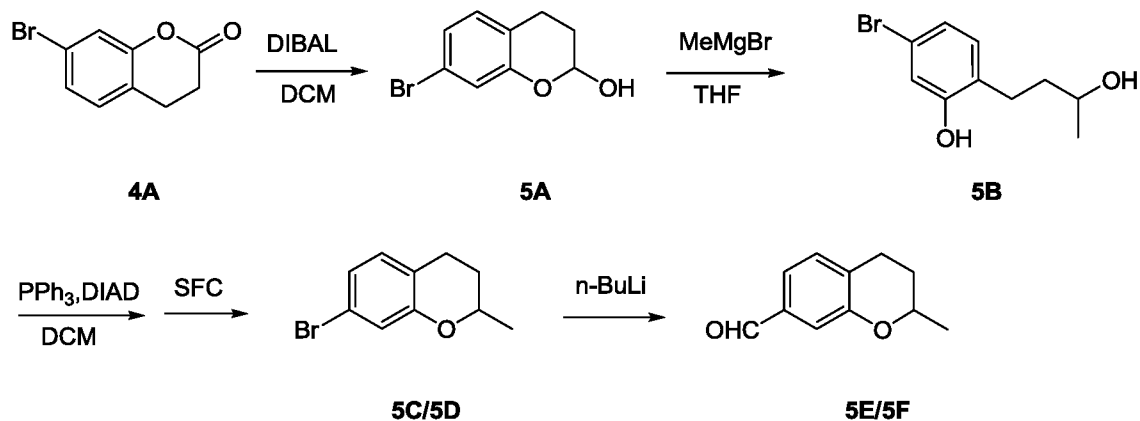
Step 2

To a solution of compound **4B** (590 mg, 2.46 mmol) in THF (10 mL) at -78°C was added n-BuLi (2.5 M in hexane, 3 mL, 7.5 mmol) dropwise under

25 nitrogen. The mixture was allowed to stir at -78°C for 10 minutes, then DMF (1.2 mL, 15.6 mmol) was added. The resultant mixture was allowed to stir at -78°C for 1 hour, then the reaction was quenched by addition of 1N aq. HCl, then extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue obtained was purified using flash

30 column chromatography on silica gel (petroleum ether: ethyl acetate = 20: 1) to provide compound **4C** as an oil. MS (ESI) m/z: 191.0 [M+H]⁺.

Example 5Preparation of Intermediate Compound **5H**



Step 1

To a solution of compound **4A** (16 g, 70.8 mmol) in DCM (200 mL) at -78°C was added DIBAL (1 M in toluene, 85 mL, 85 mmol) dropwise under nitrogen over a period of 15 minutes. The mixture was allowed to stir at -78°C for 2 hours, then was poured into 200 mL of 1 M aq. HCl, and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 20: 1 to provide compound **5A** as a solid. ¹H-NMR (CDCl₃, 400 MHz): δ 6.81-6.98 (m, 3H), 5.54 (s, 1H), 2.79-2.99 (m, 1H), 2.49-2.64 (m, 1H), 1.85-2.01 (m, 2H).

Step 2

To a solution of compound **5A** (11.5 g, 50.4 mmol) in THF (200 mL) at 0°C was added MeMgBr (3 M in Et₂O, 50.4 mL, 151 mmol) dropwise under nitrogen. The mixture was allowed to stir at 0°C for 20 minutes. The resultant mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction was then quenched by addition 1N aq. HCl, extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to provide compound **5B** as a solid. ¹H-NMR (CDCl₃, 400 MHz): δ 6.89-7.06 (m, 3H), 3.69-3.79 (m, 1H), 2.77-2.87 (m, 1H), 2.59-2.62 (m, 1H), 1.61-1.83 (m, 2H), 1.16-1.25 (m, 3H).

Step 3

5 To a solution of compound **5B** (8.2 g, 33.6 mmol) and PPh₃ (9.69 g, 37 mmol) in DCM (150 mL) at 0°C was added DIAD (7.3 mL, 37 mmol) dropwise. The mixture was allowed to stir at 0°C for 1 hour, then the reaction was quenched by addition of ice water, and extracted with DCM. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue
10 obtained was purified using flash column chromatography on silica gel (petroleum ether) to provide a mixture of isomeric compounds **5C** and **5D** as an oil, which was separated using SFC to provide isolated compounds **5C** and **5D**. Condition of SFC: Column: AD-3 (150x4.6 MM), Co-solvent: MeOH (0.05%DEA, 5-40%), flow rate: 25 mL/min.

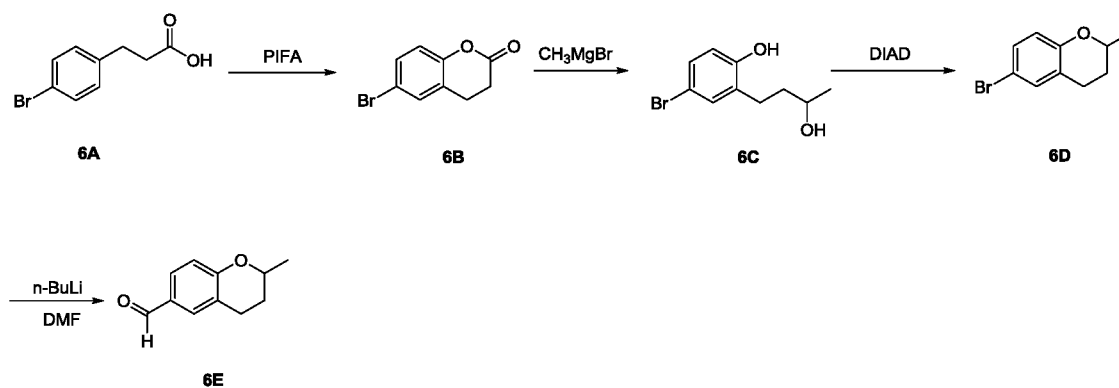
15 *Step 4*

To a solution of compound **5C** (1.108 g, 4.9 mmol) in THF (50 mL) at -78°C was added n-BuLi (2.5 M in hexane, 6 mL, 15 mmol) dropwise under nitrogen. The mixture was allowed to stir at -78°C for 10 minutes, then DMF (2.3 mL, 30 mmol)
20 was added. The resultant mixture was allowed to stir at -78°C for 1 hour, then the reaction was quenched by addition of aq. NH₄Cl, and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 20: 1 to provide
25 compound **5E** as an oil.

Compound **5F** was prepared from compound **5D** using the methodology described in Step 4 immediately above.

30 **Example 6**

Preparation of Intermediate Compound **6E**



Step 1

To a mixture of compound **6A** (70.2 g, 308 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (66 g, 462 mmol) in TFA, was added PIFA (198.6 g, 462 mmol) dropwise. The mixture was allowed to stir at 40 °C for 45 hours, and then TFA was removed in vacuo. The mixture was poured into H_2O , and extracted with ethyl acetate. The organic extract was washed with NaHCO_3 solution and brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue obtained was purified using flash column chromatography (petroleum ether:ethyl acetate=20:1~10:1) to provide compound **6B**.

Step 2

To a mixture of compound **6B** (3.41 g, 14.956mmol) in THF at 0 °C was added CH_3MgBr (32.9 mmol). The mixture was allowed to stir at 0~20 °C for 16 hours, and then the mixture was quenched with NH_4Cl , and extracted with ethyl acetate. The organic extract was washed with H_2O and brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue obtained was purified using flash column chromatography (petroleum ether:ethyl acetate= 20:1~5:1) to provide compound **6C**.

Step 3

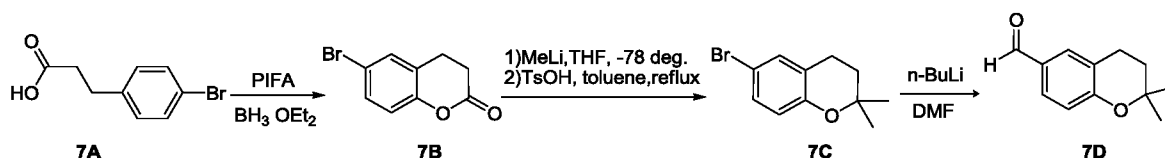
To a mixture of compound **6C** (3.05 g, 12.5 mmol) in and PPh_3 (4.912 g, 18.75 mmol) in DCM, then DIAD (4.84 g, 18.75 mmol) was added dropwise at 0°C. The mixture was allowed to stir at 0~20 °C for 2 hours, then the reaction was quenched with H_2O , extracted with ethyl acetate. The organic extract was washed with H_2O and NaCl , dried over Na_2SO_4 . After filtration and concentration, the residue obtained was purified using flash column chromatography (petroleum ether:ethyl acetate=2001~30:1) to provide compound **6D**.

5

Step 4

To a mixture of compound **6D** (2.7 g, 11.947 mmol) in THF was added n-BuLi (13.75 mmol) at -78 °C. The mixture was allowed to stir at -78 °C for 5min, and then DMF (1.3 g, 18 mmol) was added dropwise. After stirring for 30 minutes, reaction mixture was quenched with NH₄Cl, extracted with ethyl acetate. The organic extract was washed with H₂O and brine, dried over Na₂SO₄. After filtration and concentration, the residue obtained was purified using flash column chromatography (petroleum ether:ethyl acetate=100:1~30:1) to provide racemic compound **6E**. (ESI) m/z: 177.1 [M+H]⁺.

15

Example 7Preparation of Intermediate Compound **7D**

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Step 1

To a solution of compound **7A** (37 g, 162.28 mmol) and PIFA (104.67 g, 243.42 mmol) in TFA (500 mL) was added BF₃·OEt₂ (34.57 g, 243.42 mmol) dropwise at room temperature under nitrogen. The mixture was allowed to stir at 40-60 °C for 48 hours, then concentrated in vacuo. The residue obtained was dissolved in ethyl acetate, basified to pH 13 using aq. NaOH, and filtered. The filtrate was extracted with ethyl acetate and the organic extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 10: 1 to provide compound **7B** as a solid. MS (ESI) m/z: 227.1 [M+H]⁺

30

Step 2

To a solution of compound **7B** (1.12 g, 5 mmol) in THF (10 mL) at 0 °C was added MeLi (1.6 M in ether, 7.8 mL, 12.5 mmol) dropwise under nitrogen. The mixture was allowed to stir at room temperature for 16 hours, re-cooled to 0 °C using an ice bath, and aq. 1M HCl (2.5 mL) was added dropwise. The layers were separated,

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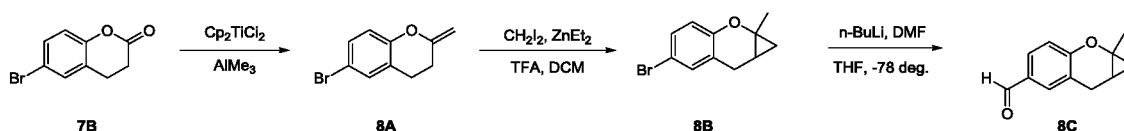
and the aqueous layer was extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue obtained was dissolved in toluene (20 mL), TsOH.H₂O (19 mg, 0.1 mmol) was added, and the mixture was refluxed for 16 hours in a Dean-Stark apparatus. After removed of the solvent in vacuo, the residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 100: 1) to provide compound **7C** as an oil. ¹H-NMR (CDCl₃, 400 MHz): δ 7.07-7.09 (m, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 2.66 (t, *J* = 6.8 Hz, 2H), 1.70 (t, *J* = 6.8 Hz, 2H), 1.24 (s, 6H).

Step 3

To a solution of compound **7C** (390 mg, 1.64 mmol) in THF (10 mL) was added n-BuLi (2.5 M in hexane, 1.96 mL, 4.92 mmol) dropwise at -78°C under nitrogen. The mixture was allowed to stir at -78°C for 10 minutes. Then DMF (0.76 mL, 9.83 mmol) was added. The resultant mixture was allowed to stir at -78°C for 1 hour. The reaction was quenched by addition aq. NH₄Cl, extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo, and the residue obtained was purified using pre-TLC eluting with petroleum ether : ethyl acetate = 20 : 1 to provide compound **7D** as an oil. ¹H-NMR (CDCl₃, 400 MHz): δ 9.76 (s, 1H), 7.54-7.56 (m, 2H), 6.79 (d, *J* = 8.8 Hz, 1H), 2.77 (t, *J* = 6.4 Hz, 2H), 1.78 (t, *J* = 6.4 Hz, 2H), 1.30 (s, 6H).

Example 8

Preparation of Intermediate Compound **8C**



Step 1

A trimethylaluminum solution (2.0 M in toluene, 20 mL, 40 mmol) at 0°C was added dropwise to Cp_2TiCl_2 (5 g, 20 mmol) under nitrogen. After the addition, the resulting solution was allowed to stir at room temperature for 24 hours, then was cooled in a dry ice-acetone bath. A solution of compound **7B** (4.48 g, 20 mmol) in THF (20 mL) was added dropwise by syringe to the cooled stirring solution over 5-10 minutes. After the addition, the reaction mixture was allowed to warm to

5 room temperature and stirred for 30 minutes. 50 drops of aq 1M NaOH was added over 10 minutes, and stirring continued until gas evolution essentially ceased. The reaction mixture was filtered, and concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether) to provide compound **8A** as an oil. ¹H-NMR (CDCl₃, 400 MHz): δ 7.17-7.24 (m, 2H), 6.75 (d, J = 8.8 Hz, 1H), 4.56 (s, 1H), 4.16 (s, 1H), 2.76 (t, J = 6.8 Hz, 2H), 2.54 (t, J = 6.8 Hz, 2H).

Step 2

CH₂I₂ (12.44 g, 46.4 mmol) was added dropwise to a -78°C stirred solution of ZnEt₂ (1 M in hexane, 23.2 mL, 23.2 mmol) in dichloromethane (23 mL) under nitrogen, and the mixture was allowed to stir at 0°C for 15 minutes resulting in the formation of a white precipitate. TFA (2.646 g, 23.2 mmol) was added to the mixture resulting in the rapid formation of a homogeneous solution which was allowed to stir at 0°C for 15 minutes. A solution of compound **8A** (2.6 g, 11.6 mmol) in dichloromethane (10 mL) was then added and the resultant mixture was allowed to stir at room temperature for 16 hours. Saturated Na₂EDTA (50 mL) was then added, and the resultant mixture was vigorously stirred for 5 minutes, then diluted with dichloromethane (100 mL) and saturated aq. NaHCO₃ (100 mL). The aqueous layer was extracted with dichloromethane and the organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel (petroleum ether) to provide compound **8B** as a solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.11-7.16 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 3.08-3.13 (m, 1H), 2.86-2.90 (m, 1H), 1.54 (s, 3H), 1.20-1.25 (m, 1H), 0.92-0.95 (m, 1H), 0.54-0.58 (m, 1H).

Step 3

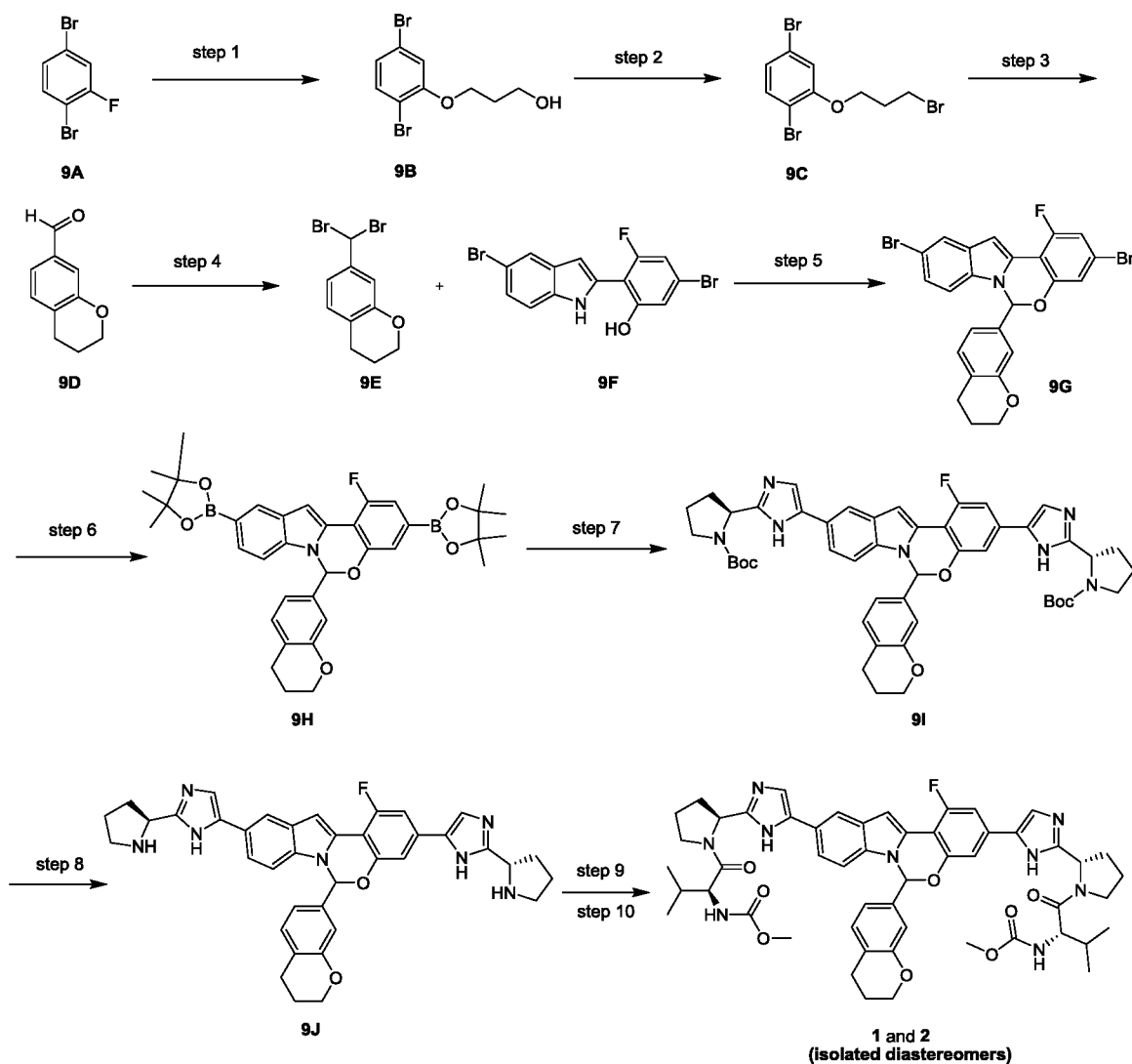
To a solution of compound **8B** (0.8 g, 3.36 mmol) in THF (20 mL) at -78°C was added n-BuLi (2.5 M in hexane, 4 mL, 10 mmol) dropwise under nitrogen. The mixture was allowed to stir at -78°C for 5 minutes, then DMF (1.54 mL, 20 mmol) was added. The resultant mixture was allowed to stir at -78°C for 1 hour and the reaction was quenched by addition aq. NH₄Cl, and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and

- 5 concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate = 100: 1 to provide compound **8C** as an oil. ¹H-NMR (CDCl₃, 400 MHz): δ 9.75 (s, 1H), 7.50-7.57 (m, 2H), 6.82 (d, J = 8.4 Hz, 1H), 3.11-3.16 (m, 1H), 2.95-2.99 (m, 1H), 1.54 (s, 3H), 1.23-1.28 (m, 1H), 0.88-0.94 (m, 1H), 0.58-0.62 (m, 1H).

10

Example 9

Preparation of Compounds **1** and **2**



15

Step 1

To a mixture of compound **9A** (20 g, 78.7 mmol), ethylene glycol (110 mL) and NMP (10 mL) was added t-BuOK (31.2 g, 280 mmol) slowly. The mixture was heated to 100 °C overnight. The mixture was poured into ice water, and extracted

- 5 with ethyl acetate. The organic extract was washed with brine, dried and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel to provide **9B** as an oil. MS (ESI): m/e 311 $[M+H]^+$.

Step 2

- 10 To a solution of compound **9B** (17 g, 54.8 mmol) in toluene (200 mL) was added PBr_3 (7.4 g, 27.4 mmol) below 0 °C, and the mixture was heated to 100 °C for 2 hours. TLC showed the compound **2** was consumed up. The mixture was poured into ice-water and extracted with ethyl acetate. The organic phase was washed with $NaHCO_3$ and brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification
- 15 using flash column chromatography on silica gel provided compound **9C** as an oil. 1H -NMR ($CDCl_3$) δ : 7.35 - 7.37 (d, J = 8.4 Hz, 1 H), 7.01 - 7.02 (m, 1 H), 6.95 - 6.98 (m, 1 H), 4.11-4.14 (t, J = 5.6 Hz, 2 H), 3.63 - 3.66 (t, J = 6.4 Hz), 2.32 - 2.38 (m, 2 H).

20 *Step 3*

- To a solution of compound **9C** (16.6 g, 50.6 mmol) in dry THF (300 mL) was added $n-BuLi$ (20 mL, 2.5 M, 50.6 mmol) at -78 °C dropwise, and stirred at this temperature for 30 minutes. Then, another batch of $n-BuLi$ (20 mL, 2.5 M, 50.6 mmol) was added dropwise. After stirring for 15 minutes, a solution of DMF (7.3 g,
- 25 100 mmol) in THF (20 mL) was added dropwise. The mixture was warmed back to RT slowly and stirred for 30 minutes. A saturated aqueous NH_4Cl was added to quench the reaction. The mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification using flash column chromatography on silica gel provided **9D** as a solid. 1H -NMR
- 30 ($CDCl_3$) δ : 9.85 (s, 1 H), 7.30 - 7.32 (m, 1 H), 7.23-7.24 (m, 1 H), 7.13-7.15 (m, 1 H), 4.17 - 4.20 (t, J = 5.2 Hz, 2 H), 1.98 - 2.03(m, 2 H).

Step 4

- To a solution of triphenyl phosphite (11.3 g, 43.2 mmol) in dry DCM
- 35 (150 mL) was added dropwise bromine (6.87 g, 43.2 mmol) at -15 °C. After 30 minutes, a solution of compound **9D** (3.5 g, 21.6 mmol) in DCM (15 mL) was added dropwise. The reaction mixture was allowed to stir at room temperature overnight. The mixture was concentrated in vacuo, and the residue obtained was purified using

- 5 flash column chromatography on silica gel to provide **9E** as a solid. $^1\text{H-NMR}$ (CDCl_3) δ : 6.98 - 7.01 (m, 3 H), 6.54 (s, 1 H), 4.16 - 4.19 (t, $J = 5.2$ Hz, 2 H), 2.76 - 2.79 (t, $J = 6.4$ Hz, 2 H), 1.95 - 2.01 (m, 2 H).

Step 5

- 10 A mixture of compound **9E** (862 mg, 2.24 mmol), **9F** (760 mg, 2.5 mmol), and K_2CO_3 (10 mmol) in 11 mL of DMF was heated to 100 °C for 3 hours. The mixture was concentrated in vacuo, and dissolved with DCM and water. The aqueous phase was extracted with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was
- 15 purified using flash column chromatography on silica gel to provide compound **9G**. $^1\text{H-NMR}$ (CDCl_3 , 400) δ : 7.79 (s, 1 H), 7.20 - 7.22 (m, 1 H), 7.07 (s, 1 H), 6.97 - 7.01 (m, 3 H), 6.90 - 6.92 (m, 1 H), 6.39 - 6.45 (m, 1 H), 6.39 (s, 1 H), 4.08 - 4.11 (t, $J = 4.8$ Hz, 1 H), 2.68 - 2.71 (t, $J = 6.4$ Hz, 2 H), 1.90 - 1.95 (m, 2 H).

20 *Step 6*

- To a solution of compound **9G** (900 mg, 1.7 mmol) in 1,4-dioxane was added bis pinacolato borate (2.0 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.09 mmol) and KOAc (5.1 mmol). The reaction mixture was allowed to stir under N_2 and heated to 110°C for about 15 hours. The reaction mixture was then concentrated in vacuo, and the residue
- 25 obtained was purified using flash column chromatography on silica gel to provide compound **9H**. MS (ESI): m/z 624 $[\text{M}+\text{H}]^+$.

Step 7

- A suspension of compound **9H** (1140 mg, 1.83 mmol), Br-imidazole-1
- 30 (2.2 mmol), $\text{Pd}(\text{dppf})_2\text{Cl}_2$ (0.1 mmol), Na_2CO_3 (5.5 mmol) and in THF/ H_2O (10:1, 10 mL) was refluxed at 75°C overnight under N_2 . The mixture was then filtered, and the filtrate was washed with water (50 mL) and extracted with ethyl acetate (100 mL), and the organic extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue obtained was purified using flash column
- 35 chromatography on silica gel (petroleum ether / ethyl acetate = 8:1 to 5:1) to provide compound **9I**. MS (ESI) m/e ($\text{M}+\text{H}^+$): 842.

Step 8

5 Compound **9I** (400 mg, 0.48 mmol) was added into a solution of HCl/CH₃OH (5 mL, 3M) and the resulting reaction was allowed to stir at room temperature for 3 hours. The reaction mixture was then concentrated in vacuo to provide compound **9J**, which was used without further purification. MS (ESI) *m/z* (M+H⁺): 642.

10 *Step 9*

To a mixture of compound **9J** (355 mg, 0.45 mmol), **cap-1** (0.99 mmol) and DIPEA (3.6 mmol) in DMF (5 mL) was added HATU (1.0 mmol). The resulting mixture was allowed to stir at room temperature until LCMS showed that the starting material was completely consumed. The reaction mixture was then directly purified using preparative HPLC to provide a racemic mixture of compounds **1** and **2**. ¹H-NMR (MeOD 400MHz) δ : 7.90 - 7.96 (m, 1 H), 7.80 - 7.81 (m, 1 H), 7.41 - 7.45 (m, 1 H), 7.25 - 7.37 (m, 3 H), 7.09 - 7.19 (m, 3 H), 6.88 - 6.92 (m, 1 H), 6.43 - 6.59 (m, 1 H), 6.28 (s, 1 H), 5.15 - 5.24 (m, 2 H), 4.19 - 4.23 (m, 2 H), 4.02 - 4.09 (m, 4 H), 3.94 - 3.95 (m, 2 H), 3.64 (s, 6 H), 2.64 - 2.65 (m, 2 H), 2.52 - 2.55 (m, 2 H), 2.01 - 2.26 (m, 8 H), 1.85 - 1.89 (m, 2 H), 0.97 - 0.94 (m, 12 H). MS (ESI) *m/z* (M+H⁺): 956.5.

Step 10

A racemic mixture of Compounds **1** and **2** was separated using chiral SFC to provide pure diastereomers **1** and **2**. SFC: Column: Chiralpak AS-H, 250×20 mm, 5 μ m, Mobile phase: 40% of EtOH (0.05%DEA) in CO₂, Flow rate: 50 mL/min, wavelength: 220 nm.

1: ¹H-NMR (MeOH-d₄, 400MHz) δ : 7.99 (s, 1 H), 7.84 (s, 1 H), 7.40 - 7.44 (m, 2 H), 7.22 - 7.27 (m, 3 H), 7.14 - 7.15 (m, 1 H), 6.90 - 6.92 (m, 1 H), 6.43 - 6.45 (m, 1 H), 6.30 (s, 1 H), 5.16 - 5.25 (m, 2 H), 4.18 - 4.23 (m, 2 H), 4.02 - 4.07 (m, 4 H), 3.83 - 3.88 (m, 2 H), 3.64 (s, 6 H), 2.63 - 2.67 (m, 2 H), 2.50 - 2.54 (m, 2 H), 2.24 - 2.26 (m, 2 H), 2.13 - 2.19 (m, 4 H), 2.01 - 2.08 (m, 2 H), 1.85 - 1.87 (m, 2 H). MS (ESI) *m/z* (M+H⁺): 956.5.

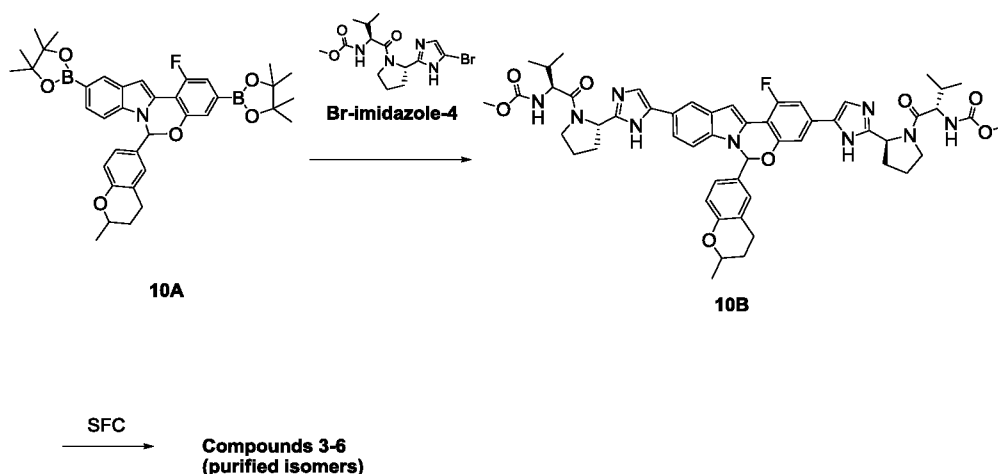
2: ¹H-NMR (MeOH-d₄, 400MHz) δ : 7.92 (s, 1 H), 7.81 (s, 1 H), 7.69 (s, 1 H), 7.41 - 7.46 (m, 2 H), 7.25 - 7.28 (m, 2 H), 7.14 (m, 1 H), 7.08 - 7.09 (m, 1 H), 6.88 - 6.90 (m, 1 H), 6.40 - 6.42 (m, 1 H), 6.29 (s, 1 H), 5.17 - 5.23 (m, 2 H), 4.20 - 4.24 (m, 2 H),

- 5 4.00 - 4.08 (m, 4 H), 3.85 - 3.89 (m, 2 H), 3.63 (s, 6 H), 2.62 - 2.64 (m, 2 H), 2.48 - 2.57 (m, 2 H), 2.21 - 2.32 (m, 2 H), 2.05 - 2.17 (m, 6 H), 0.86 - 0.96 (m, 12 H). MS (ESI) m/z ($M+H^+$): 956.6.

Example 10

10

Preparation of Compounds 3-6



Step 1

- A suspension of compound **10A** (made using the methodology described in Example 9 to provide intermediate compound **9H**, 500 mg, 0.79 mmol),
- 15 **Br-imidazole-4** (600 mg, 1.6 mmol), $\text{Pd(dppf)}_2\text{Cl}_2$ (60 mg, 0.08 mmol) and Na_2CO_3 (400 mg, 3.6 mmol) in THF/ H_2O (10:1, 70 mL) was allowed to stir at reflux for about 15 hours under N_2 . The reaction mixture was filtered, and the filtrate was washed with water (100 mL) and extracted with ethyl acetate (200 mL). The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in
- 20 vacuo. The residue obtained was purified using HPLC (acidic) to provide **10B** as a mixture of four isomers.

Step 2

- Isomeric mixture **10B** was resolved using chiral SFC to provide the
- 25 four purified diastereomers as compounds **3-6**. Conditions: Chiralpak AS-H 250×20 mm, 5 μm Mobile phase: 40% of EtOH (0.05% DEA) in CO_2 , Flow rate: 50 mL/min, wavelength: 220 nm.

- 3**: $^1\text{H-NMR}$ (MeOH-d_4 , 400MHz) δ : 8.00 (s, 1 H), 7.85 (s, 1 H), 7.73 (s, 1 H), 7.434 -
- 30 7.135 (m, 6 H), 6.79 - 6.74 (m, 2 H), 6.64 - 6.62 (d, 1 H), 5.26 - 5.17 (m, 2 H), 4.24 -

5 4.20 (m, 2 H), 4.10- 4.04 (m, 3 H), 3.88- 3.84 (m, 2 H), 3.65-3.65 (m, 6 H), 2.70-2.51 (m, 4 H), 2.25-1.93 (m, 7 H), 1.02-1.51 (m, 1H), 1.37-1.30 (m, 3H), 0.94 - 0.87 (m, 12 H). MS (ESI) m/z : 970.7 [M+H]⁺:

4: ¹H-NMR (MeOH-d₄, 400MHz) δ: 7.94 (s, 1 H), 7.70 (s, 2 H), 7.42 - 7.27 (m, 3 H),
10 7.15-7.11 (m, 3H), 6.76 - 6.73 (m, 2 H), 6.62- 6.60 (d, 1 H), 5.24 - 5.16 (m, 2 H), 4.20 (m, 2 H), 4.08- 4.03 (m, 3 H), 3.85 (m, 2 H), 3.63 (m, 6 H), 2.76-2.67 (m, 1 H), 2.57- 2.43 (m, 3 H), 2.24-1.91 (m, 9H), 1.58-1.48 (m, 1H), 1.29-1.28 (m, 3H), 0.99- 0.88 (m, 12 H). MS (ESI) m/z : 970.7 [M+H]⁺.

15 5: ¹H-NMR (MeOH-d₄, 400MHz) δ: 7.95 (s, 1 H), 7.78 (s, 1 H), 7.71 (s, 1 H), 7.43 - 7.28 (m, 3 H), 7.17-7.14 (m, 3H), 6.76-6.71 (m, 2 H), 6.62 - 6.59 (d, 1 H), 5.24-5.15 (m, 2 H), 4.23-4.19 (m, 2 H), 4.07-4.02 (m, 3 H), 3.87-3.85 (m, 2 H), 3.63 (m, 6 H), 2.68-2.46 (m, 4 H), 2.24-1.9 (m, 9 H), 1.59-1.52 (m, 1H), 1.29-1.28 (m, 3H), 0.93- 0.86 (m, 12 H). MS (ESI) m/z: 970.7 [M+H]⁺.

20

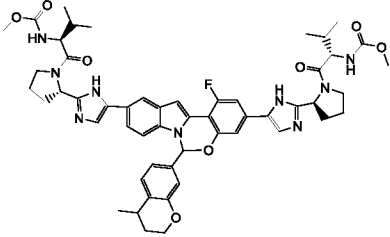
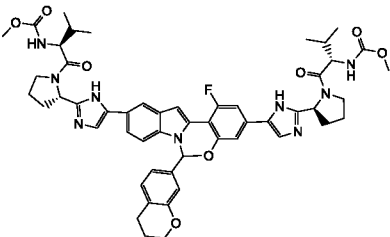
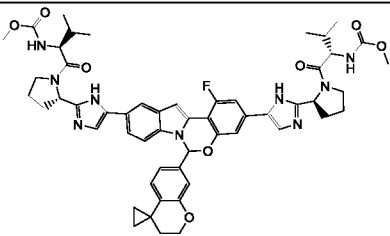
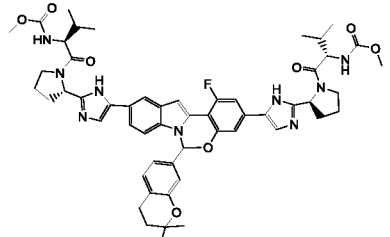
6: ¹H-NMR (MeOH-d₄, 400MHz) δ: 7.98 (s, 1 H), 7.86 (s, 1 H), 7.72 (s, 1 H), 7.41 - 7.27 (m, 3 H), 7.22-7.10 (m, 3H), 6.77-6.74 (m, 2 H), 6.64-6.61 (d, 1 H), 5.24-5.16 (m, 2 H), 4.23-4.18 (m, 2 H), 4.07-4.03 (m, 3 H), 3.87-3.83 (m, 2 H), 3.64 (m, 6 H), 2.73 - 2.51 (m, 4 H), 2.24-1.92 (m, 9 H), 1.57-1.53 (m, 1H), 1.30-1.28 (m, 3H), 0.93- 0.86
25 (m, 12 H). MS (ESI) m/z: 970.7 [M+H]⁺.

The following compounds of the present invention were made using the methods described in the Example above, and substituting the appropriate reagents and/or reactants:

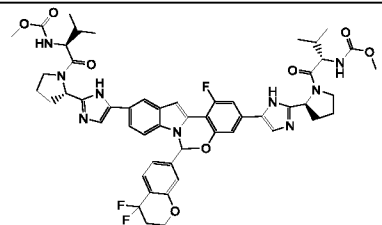
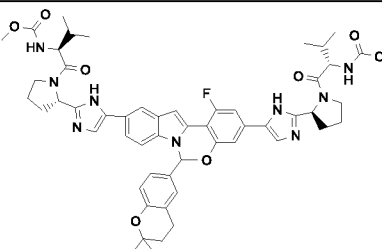
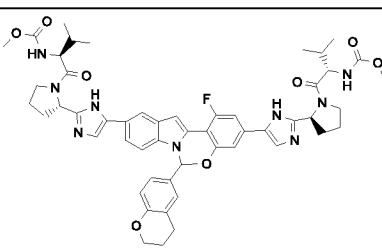
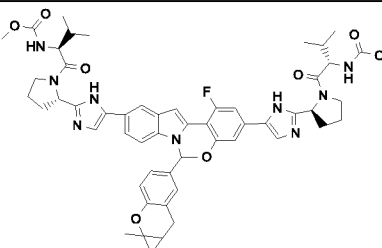
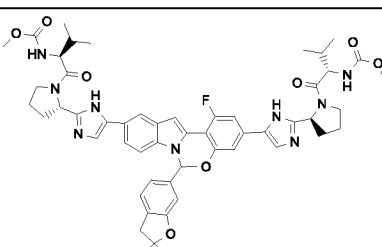
30

35

	Structure	Isomer	Observed [M+H] ⁺

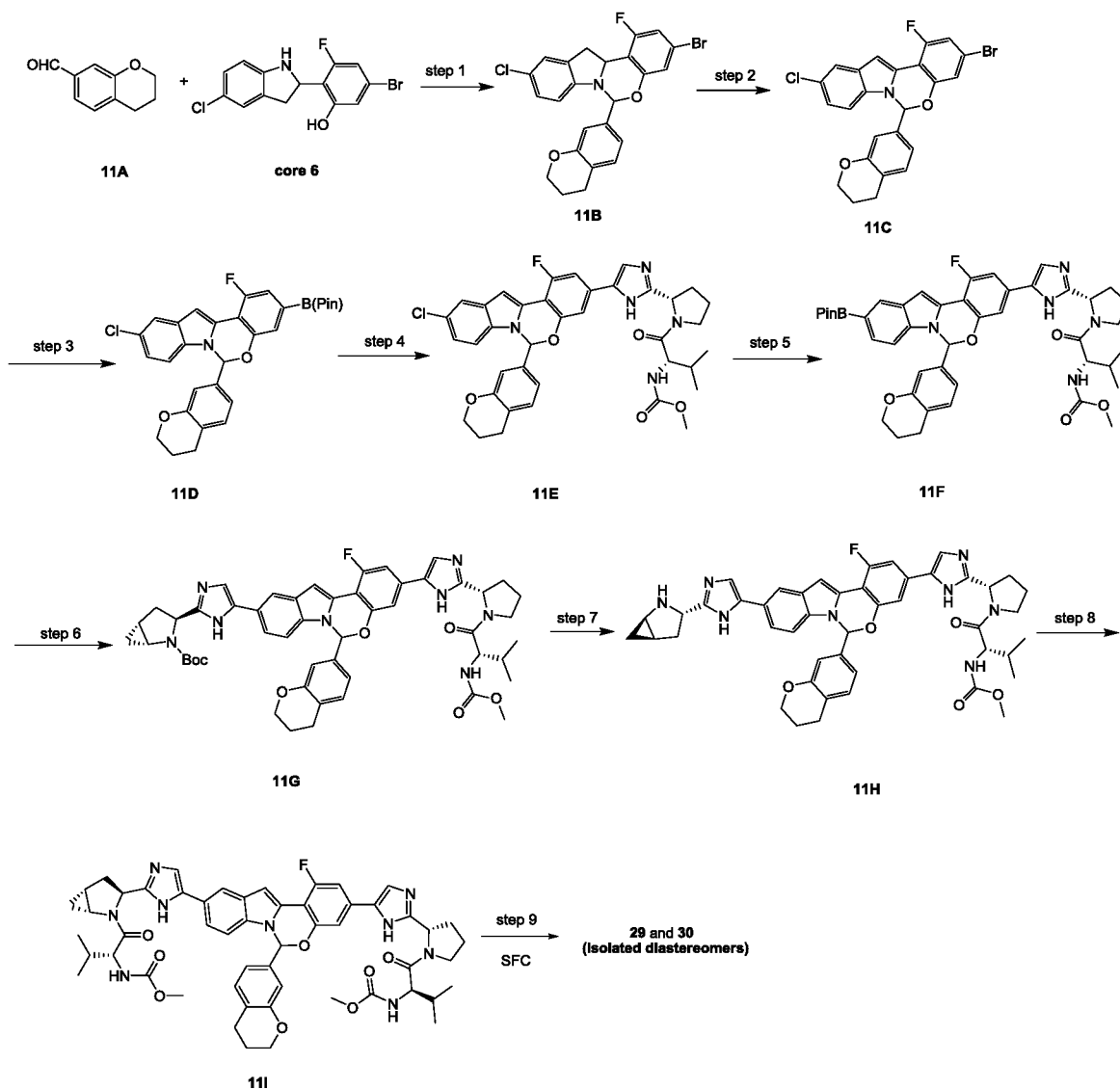
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8		Isomer 2	970.5
9		Isomer 3	970.6
10		Isomer 4	970.6
11		Isomer 1	970.5
12		Isomer 2	970.5
13		Isomer 3	970.5
14		Isomer 4	970.5
15		Isomer 1	982.4
16		Isomer 2	982.5
17		Isomer 1	984.5
18		Isomer 2	984.5

5

19		Isomer 1	92.4
20		Isomer 2	92.4
21		Isomer 1	84.6
22		Isomer 2	84.6
23		Isomer 1	56.9
24		Isomer 2	56.9
25		Isomer 1	82.5
26		Isomer 2	82.5
27		Isomer 1	70.5
28		Isomer 2	70.5

Example 10**Preparation of Compounds 29-30**

10



5

Step 1

To a mixture of compound **11A** (20 g, 0.12 mole) and **core 6** (38 g, 0.12 mole) in anhydrous CH_3CN (400 mL) was added TFA (0.1 mL) at room temperature. The mixture was agitated for 6 hours at room temperature and the solid formed was collected by filtration and washed with CH_3CN to provide compound **11B**.

Step 2

To a solution of compound **11B** (48 g, 98.6 mmol) in dry toluene (450 mL) was added DDQ (33.6 g, 0.15 mole). The reaction was allowed to stir at reflux for 2 hours, then concentrated in vacuo and the resulting residue was diluted with EtOAc. The resulting solution was washed with saturated NaS_2O_3 aqueous and brine,

- 5 dried over Na₂SO₄, filtered and concentrated in vacuo. The residue obtained was washed with MeOH, filtered and the collected solid was dried in vacuo to provide compound **11C** (45 g, 93% yield).

Step 3

- 10 To a solution of compound **11C** (21.3 g, 44 mmol) in 1,4-dioxane (350 mL) was added bis pinacolato borate (13.4 g, 52.7 mmol) and Pd(dppf)Cl₂ (3.2 g, 4.4 mmol) and KOAc (8.6 g, 87.8 mmol). The reaction mixture was allowed to stir under N₂ and heated to 110°C for about 15 hours. The reaction mixture was then concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel to provide compound **11D** (22 g, 94% yield).

Step 4

- A suspension of compound **11D** (22 g, 41.4 mmol), **Cap 7** (17 g, 45 mmol), Pd(dppf)Cl₂ (3 g, 4.1 mmol) and Na₂CO₃ (8.8 g, 82.7 mmol) in THF-H₂O (150 -60 mL) was stirred at reflux for 15 hours under N₂. The reaction mixture was then filtered, and the filtrate was washed with water and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel to provide **11E** (24.1 g, 83.6% yield).

25

Step 5

- To a solution of compound **11E** (24.1 g, 34.6 mmol) in 1,4-dioxane (300 mL) was added bis pinacolato borate (10.5 g, 41.2 mmol), X-phos (3.3 g, 6.9 mmol) and Pd₂(dba)₃ (3.2 g, 3.4 mmol) and KOAc (6.8 g, 69.2 mmol). The reaction mixture was allowed to stir at reflux under N₂ for about 15 hours. The reaction mixture was then concentrated in vacuo, and the residue obtained was purified using flash column chromatography on silica gel (petroleum ether: ethyl acetate= 1:1) to provide the compound **11F** (22 g, 80.6% yield).

30

Step 6

- A suspension of compound **11F** (3 g, 3.8 mmol), **Br-imidazole-2** (1.37 g, 4.18 mmol), Pd(dppf)Cl₂ (278 mg, 2.38 mmol) and Na₂CO₃ (807 mg, 7.6 mmol) in THF-H₂O (25 -10 mL) was allowed to stir at reflux under N₂ for about 15 hours. The

35

5 reaction mixture was then filtered, and the filtrate was washed with water and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue obtained was purified using flash column chromatography on silica gel to provide **11G** (1.9 g, 55% yield).

10

Step 7

A mixture of compound **11G** (910 mg, 1mmol) in HCl-MeOH (10 mL) was allowed to stir at 25°C for 30 minutes, and was then concentrated in vacuo to provide the crude compound **11H** (810 mg, 100% yield).

15

Step 8

To a solution of (R)-2-((methoxycarbonyl)amino)-3-methylbutanoic acid (173 mg, 1 mmol) and DIPEA (358 mg, 2 mmol) in DMF (10 mL) was added HATU (380 mg, 1 mmol). The mixture was allowed to stir at 25 °C for 20 minutes, then compound **11H** (810 mg, 1 mmol) was added. The reaction was allowed to stir at 25 °C for 30 minutes, then filtered. The reaction mixture was directly purified using prep-HPLC to provide a racemic mixture of diastereomers **29** and **30** (520 mg, 53.7% yield).

25 *Step 9*

A racemic mixture of diastereomers **29** and **30** was resolved using chiral SFC to provide pure diastereomers **29** and **30**. Conditions: Chiralpak AS-H 250×20 mm, 5 μm Mobile phase: 40% of EtOH (0.05% DEA) in CO₂, Flow rate: 50 mL/min, wavelength: 220 nm.

30

29: ¹H-NMR (MeOH-d₄, 400MHz) δ : 8.01 (s, 1 H), 7.88 (s, 1 H), 7.71 (s, 1 H), 7.48 - 7.45 (m, 2 H), 7.33 - 7.12 (m, 4H), 6.90 - 6.88 (d, 1 H, J=8), 6.42 - 6.40 (m, 1 H), 6.29 (s, 1 H), 5.19 - 5.10 (m, 2 H), 4.54 - 4.52 (m, 1 H), 4.22 - 4.20 (m, 1 H), 4.03 - 4.00 (m, 3 H), 3.92 - 3.73 (m, 2 H), 3.64 - 3.63 (m, 6 H), 2.66 - 2.64 (m, 3H), 2.53 - 2.45 (m, 2 H), 2.26 - 2.00 (m, 6 H), 1.87 - 1.84 (m, 2 H), 1.08 - 0.86 (m, 14 H). MS (ESI): *m/z* 968.5 [M+H]⁺.

35

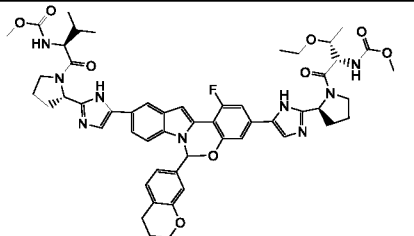
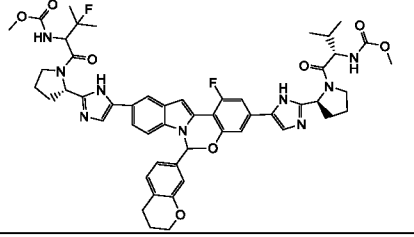
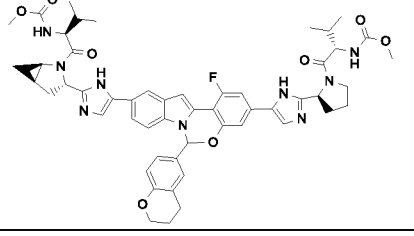
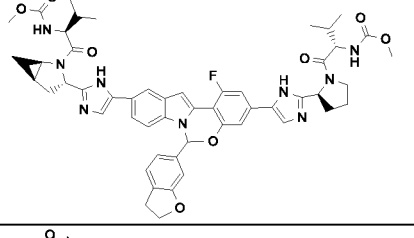
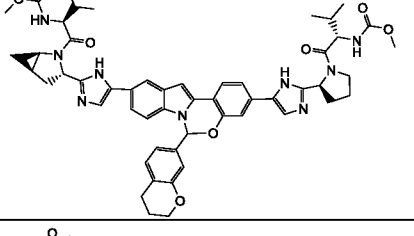
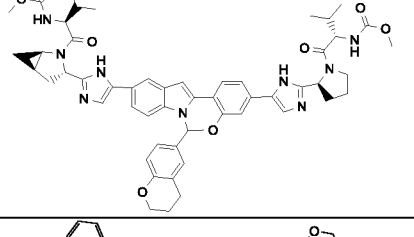
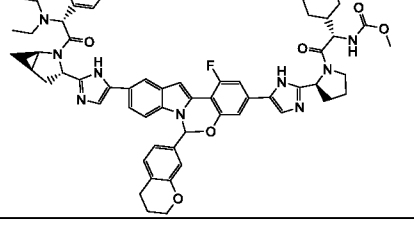
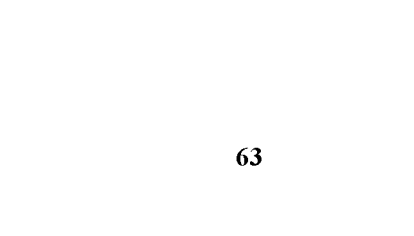
30: MS (ESI): *m/z* 968.5 [M+H]⁺.

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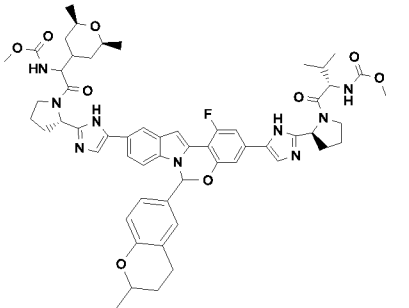
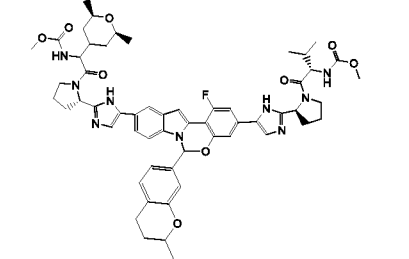
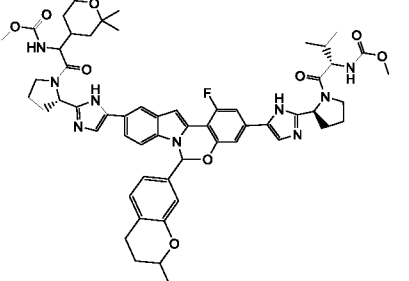
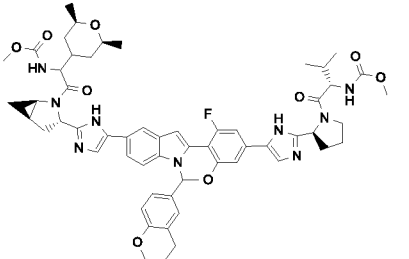
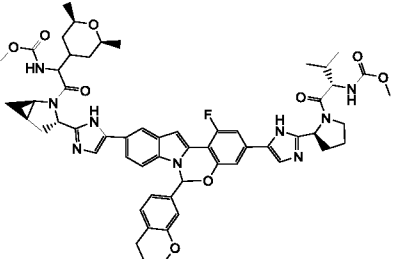
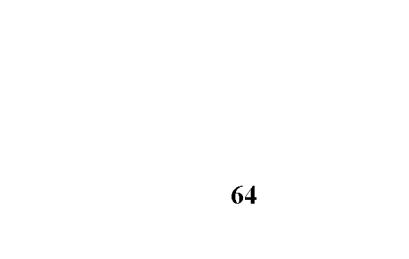
The following compounds were prepared using the methods described above and by substituting the appropriate reagents and/or reactants:

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31		Isomer 1	998.5
32		Isomer 2	998.5
33		Isomer 1	998.5
34		Isomer 2	998.6
35		Isomer 1	998.7
36		Isomer 2	998.7
37		Isomer 1	990.4
38		Isomer 2	990.4

5

39		Isomer 1	986.5
40		Isomer 2	986.9
41		Isomer 1	974.5
42		Isomer 2	974.5
43		Isomer 3	974.5
44		Isomer 4	974.5
45		Isomer 1	968.5
46		Isomer 2	968.5
47		Isomer 1	954.4
48		Isomer 2	954.4
49		Isomer 1	950.5
50		Isomer 2	950.5
51		Isomer 1	950.5
52		Isomer 2	950.5
53		Isomer 1	1042.6
54		Isomer 2	1042.6

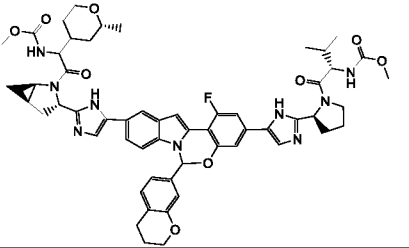
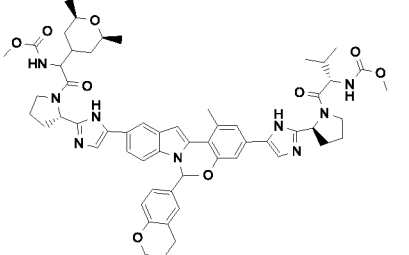
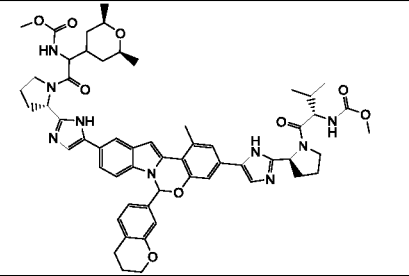
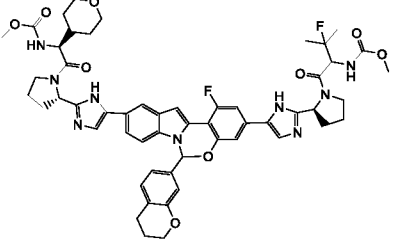
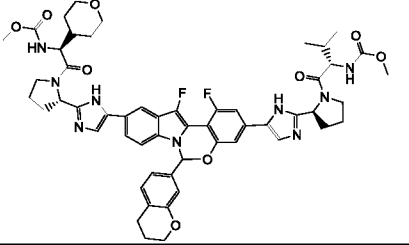
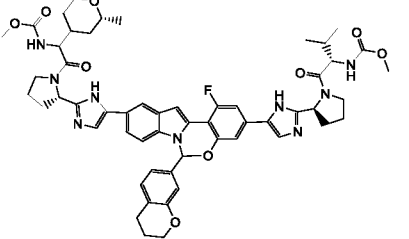
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56		Isomer 2	1040.6
57		Isomer 1	1040.6
58		Isomer 2	1040.6
59		Isomer 3	1040.7
60		Isomer 4	1040.6
61		Isomer 1	1040.6
62		Isomer 2	1040.6
63		Isomer 3	1040.6
64		Isomer 4	1040.9
65		Isomer 1	1038.5
66		Isomer 2	1038.5
67		Isomer 1	1038.9
68		Isomer 2	10.388

5

69		Isomer 1	1038.5
70		Isomer 2	1038.5
71		Isomer 1	1026.6
72		Isomer 2	1026.2
73		Isomer 1	1026.8
74		Isomer 2	1026.8
75		Isomer 1	1026.4
76		Isomer 2	1026.4
77		Isomer 1	1026.5
78		Isomer 2	1026.6
79		Isomer 1	1026.5
80		Isomer 2	1026.5

5

81		Isomer 1	1024.4
82		Isomer 2	1024.4
83		Isomer 1	1023.0
84		Isomer 2	1023.0
85		Isomer 1	1022.7
86		Isomer 2	1022.7
87		Isomer 1	1016.5
88		Isomer 2	1016.6
89		Isomer 3	1016.5
90		Isomer 4	1016.5
91		Isomer 1	1016.8
92		Isomer 2	1016.8
93		Isomer 1	1012.5
94		Isomer 2	1012.5

EXAMPLE 16**Cell-Based HCV Replicon Assays**

5 To measure cell-based anti-HCV activity of compounds of the present invention, two complimentary assays were employed using various replicons. In the first assay ("Replicon Assay A"), replicon cells were seeded at 2000 cells/well in 384-well 384-well flat bottom tissue culture treated clear bottom plate (Corning 3707) in the presence of the test compound. Various concentrations of test compound, typically in 10 serial dilutions, were added to the assay mixture, with the starting concentration ranging from 333.3 nM to 1.667 nM. The final concentration of DMSO was 0.5%. Fetal bovine serum was 5%, in the assay media. Cells were harvested on day 3 by removing media and washing the cells with a suitable wash buffer. The cells were lysed with the addition of 1x Qiagen lysis buffer (Cat #1062731). The replicon RNA level was measured using real time PCR (TaqMan® EZ RT-PCR, Applied Biosystems 403028) with the following primers and probes:

Neo Forward: CCG GCT ACC TGC CCA TTC
Neo Reverse: CCA GAT CAT CCT GAT CGA CAA G
Neo Probe: FAM-ACA TCG CAT CGA GCG AGC ACG TAC-Tamra
20 Cyc probe: 5'-JOE-CGCGTCTCCTTTGAGCTGTTTGCA-Tamra-3'
Cyc Forward Primer: ACGGCGAGCCCTTGG
Cyc Reverse Primer: TTTCTGCTGTCTTTGGGACCT

Cyclophilin RNA was used as endogenous control and was amplified in the same reaction as NS5B (multiplex PCR). The real-time RT-PCR reactions were run on ABI PRISM 7900HT Sequence Detection System using the following program: 50°C for 2 minutes, 60°C for 30 minutes, 95°C for 5 minutes, 40 cycles of 94°C for 20 sec, 55°C for 1 minutes.

The amount of HCV replicon RNA per cell was quantified using a linear regression curve for a known nanogram (ng) amount of HCV replicon total RNA. This was established by plotting the Cycle Threshold values (Ct) from the Neo probe and primer set versus the log (ng) for each HCV replicon total RNA standard. The amount of HCV RNA for each replicon sample was calculated by taking the sample's Ct value, minus the line intercept, divided by the slope of the line. Similarly, the amount of Cyclophilin mRNA per cell was also quantified using a linear regression curve for a known nanogram (ng) amount of HCV replicon total RNA. Again, this was established by plotting the Cycle Threshold values (Ct) from the Cyclophilin probe and primer set versus the log (ng) for each HCV replicon total RNA standard.

In an alternate assay ("Replicon Assay B"), 1000 cells were seeded per well in a 384-well collagen coated black plate from Greiner bio-one (Cat # 781946) in 5% FBS. Inhibitors of this invention were added at 24 h post-seeding, and the plates were incubated for 3 days. Cells were subsequently lysed with Qiagen lysis buffer (Cat #1062731) to extract the RNA. HCV replicon RNA level was measured by real-time PCR using the RNA-to-CT kit from Applied Biosystem (Cat # 4392656) and genotype-specific primers and probes. The amplicon was located within NS5B. The sequence of the PCR primers are as follows: 5B.2F, ATGGACAGGCGCCCTGA (SEQ. ID NO. 1); 5B.2R, TTGATGGGCAGCTTGTTTC (SEQ. ID NO. 2); the probe sequence was FAM-labeled CACGCCATGCGCTGCGG (SEQ. ID NO. 3). To detect genotype 1A the primer 1A F, TGC GGAACCGGTGAGTACA and 1A R, GCGGGTTTATCCAAGAAAGGA were used; the probe sequence was FAM-CGGAATTGCCAGGACGACCGG.

The real-time RT-PCR reactions were run on ABI PRISM 7900HT or Viia7 Sequence Detection System using the following program: 48°C for 30 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 sec, 60°C for 1 minutes. The 50% effective concentration (EC₅₀) was the drug concentration necessary to achieve an increase in the cycle threshold (C_T) of 1 over the projected baseline C_T. The EC₉₀ was the drug concentration necessary to achieve an increase in C_T of 3.2 over the projected baseline C_T.

Data was obtained for various compounds of the present invention using the methods described in the Example above, and is presented in the table immediately below. EC₅₀ data for replicons 1A, 1AY93H and 2B were obtained using Replicon Assay A and EC₅₀ data for replicon 1B was obtained using Replicon Assay B.

CPD	1A	1B	2a	2B	1A Y93H
Racemate of 1 and 2	0.0061			0.260	0.716
1	0.0059			0.468	4.130
2	0.0033	0.0025	0.0019	0.096	0.136
3	0.0012			4.549	11.970
4	0.0021			1.597	0.352
5	0.0024			1.273	0.130
6	0.0020			2.375	2.014

7	0.0017			1.594	2.177
8	0.0021	0.0011		0.041	0.038
9	0.0026			0.772	0.949
10	0.0024	0.0012		0.041	0.039
11	0.0025			1.391	5.702
12	0.0016			1.900	6.732
13	0.0023	0.0032		0.144	0.106
14	0.0018	0.0026		0.163	0.119
15	0.0012			1.313	2.150
16	0.0020	0.0008		0.038	0.031
17	0.0006			5.212	11.840
18	0.0022			0.252	0.052
19	0.0014			0.767	4.195
20	0.0013	0.0014		0.040	0.067
21	0.0015			3.559	7.110
22	0.0027			0.930	0.162
23	0.0020			5.165	2.622
24	0.0016			1.773	0.282
25	0.0037			3.828	4.666
26	0.0028			1.408	0.344
27	0.0014			1.481	1.085
28	0.0017	0.0021		0.105	0.032
29	0.0012			2.905	1.846
30	0.0020	0.0026	0.0002	0.093	0.017
31	0.0015	0.0022		0.098	0.322
32	0.0026	0.0026		0.003	0.010
33	0.0018	0.0021		0.114	0.598
34	0.0021	0.0030		0.005	0.008
35	0.0034	0.0012		0.258	0.061
36	0.0021			0.416	0.426
37	0.1872				15.180
38	0.0052				6.649
39	0.0017	0.0014		0.910	3.384
40	0.0021	0.0022		0.086	0.107
41				4.134	
42					
43	0.0022	0.0023		0.081	0.075
44				4.908	
45	0.0010			5.281	0.120
46	0.0026			7.708	4.127
47	0.0008			4.317	4.519
48	0.0019	0.0015		0.382	0.033
49	0.0016			0.817	2.439
50	0.0014	0.0014		0.036	0.060
51	0.0019	0.0025		4.772	2.127
52	0.0022	0.0031		1.671	0.454
53				0.379	
54	0.0049	0.0024		0.011	0.008

55	0.0019			1.257	1.864
56	0.0024			0.288	0.114
57	0.0020			0.330	0.685
58	0.0022			0.403	1.091
59	0.0032	0.0027		0.017	0.015
60	0.0030	0.0031		0.025	0.020
61	0.0023			0.215	1.486
62	0.0019			0.253	0.516
63	0.0026	0.0020		0.016	0.032
64	0.0027	0.0040		0.026	0.060
65	0.0029	0.0018		0.935	0.043
66	0.0034			2.345	0.172
67	0.0012			0.607	0.391
68	0.0018	0.0023		0.016	0.005
69	0.0032	0.0035		0.008	0.005
70	0.0028	0.0027	0.0008	0.012	0.006
71				5.133	
72				3.297	
73	0.0031			0.791	1.359
74	0.0025			0.234	0.091
75	0.0018			0.296	1.274
76	0.0025	0.0032		0.004	0.012
77	0.0015			0.099	0.496
78	0.0022	0.0026		0.004	0.009
79	0.0017	0.0027		0.007	0.006
80	0.0026	0.0032		0.006	0.024
81	0.0020			0.270	0.188
82	0.0017	0.0021		0.004	0.003
83	0.0039			0.160	0.594
84	0.0020			0.193	0.674
85	0.0027			0.070	0.575
86	0.0030	0.0027		0.007	0.028
87	0.0023	0.0034		0.133	0.528
88	0.0149	0.0026		3.114	9.934
89	0.0021	0.0031		0.015	0.017
90	0.0017	0.0032		0.157	0.047
91	0.0011			0.123	0.893
92	0.0015	0.0024		0.006	0.006
93	0.0017	0.0021		0.112	0.671
94	0.0023	0.0033		0.004	0.006

5

NOTE: Blank entries denote that data was not available.

Uses of the Chromane-Substituted Tetracyclic Compounds

10

The Chromane-Substituted Tetracyclic Compounds are useful in human and veterinary medicine for treating or preventing a viral infection in a patient. In one embodiment, the Chromane-Substituted Tetracyclic Compounds can be

5 inhibitors of viral replication. In another embodiment, the Chromane-Substituted
Tetracyclic Compounds can be inhibitors of HCV replication. Accordingly, the
Chromane-Substituted Tetracyclic Compounds are useful for treating viral infections,
such as HCV. In accordance with the invention, the Chromane-Substituted
Tetracyclic Compounds can be administered to a patient in need of treatment or
10 prevention of a viral infection.

Accordingly, in one embodiment, the invention provides methods for
treating a viral infection in a patient comprising administering to the patient an
effective amount of at least one Chromane-Substituted Tetracyclic Compound or a
pharmaceutically acceptable salt thereof.

15

Treatment or Prevention of a Flaviviridae Virus

The Chromane-Substituted Tetracyclic Compounds can be useful for
treating or preventing a viral infection caused by the Flaviviridae family of viruses.

20 Examples of Flaviviridae infections that can be treated or prevented
using the present methods include but are not limited to, dengue fever, Japanese
encephalitis, Kyasanur Forest disease, Murray Valley encephalitis, St. Louis
encephalitis, Tick-borne encephalitis, West Nile encephalitis, yellow fever and
Hepatitis C Virus (HCV) infection.

25 In one embodiment, the Flaviviridae infection being treated is hepatitis
C virus infection.

Treatment or Prevention of HCV Infection

The Chromane-Substituted Tetracyclic Compounds are useful in the
30 inhibition of HCV replication, the treatment of HCV infection and/or reduction of the
likelihood or severity of symptoms of HCV infection and the inhibition of HCV viral
replication and/or HCV viral production in a cell-based system. For example, the
Chromane-Substituted Tetracyclic Compounds are useful in treating infection by
HCV after suspected past exposure to HCV by such means as blood transfusion,
35 exchange of body fluids, bites, accidental needle stick, or exposure to patient blood
during surgery or other medical procedures.

In one embodiment, the hepatitis C infection is acute hepatitis C. In
another embodiment, the hepatitis C infection is chronic hepatitis C.

5 Accordingly, in one embodiment, the invention provides methods for treating HCV infection in a patient, the methods comprising administering to the patient an effective amount of at least one Chromane-Substituted Tetracyclic Compound or a pharmaceutically acceptable salt thereof. In a specific embodiment, the amount administered is effective to treat or prevent infection by HCV in the patient. In another specific embodiment, the amount administered is effective to inhibit HCV viral replication and/or viral production in the patient.

 The Chromane-Substituted Tetracyclic Compounds are also useful in the preparation and execution of screening assays for antiviral compounds. For example the Chromane-Substituted Tetracyclic Compounds are useful for identifying resistant HCV replicon cell lines harboring mutations within NS5A, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the Chromane-Substituted Tetracyclic Compounds are useful in establishing or determining the binding site of other antivirals to the HCV replicase.

 The compositions and combinations of the present invention can be useful for treating a patient suffering from infection related to any HCV genotype. HCV types and subtypes may differ in their antigenicity, level of viremia, severity of disease produced, and response to interferon therapy as described in Holland *et al.*, *Pathology*, 30(2):192-195 (1998). The nomenclature set forth in Simmonds *et al.*, *J Gen Virol*, 74(Pt11):2391-2399 (1993) is widely used and classifies isolates into six major genotypes, 1 through 6, with two or more related subtypes, *e.g.*, 1a and 1b. Additional genotypes 7-10 and 11 have been proposed, however the phylogenetic basis on which this classification is based has been questioned, and thus types 7, 8, 9 and 11 isolates have been reassigned as type 6, and type 10 isolates as type 3 (see Lamballerie *et al.*, *J Gen Virol*, 78(Pt1):45-51 (1997)). The major genotypes have been defined as having sequence similarities of between 55 and 72% (mean 64.5%), and subtypes within types as having 75%-86% similarity (mean 80%) when sequenced in the NS-5 region (see Simmonds *et al.*, *J Gen Virol*, 75(Pt 5):1053-1061 (1994)).

Combination Therapy

 In another embodiment, the present methods for treating or preventing HCV infection can further comprise the administration of one or more additional therapeutic agents which are not Chromane-Substituted Tetracyclic Compounds.

5 In one embodiment, the additional therapeutic agent is an antiviral agent.

 In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

 Accordingly, in one embodiment, the present invention provides
10 methods for treating a viral infection in a patient, the method comprising administering to the patient: (i) at least one Chromane-Substituted Tetracyclic Compound, or a pharmaceutically acceptable salt thereof, and (ii) at least one additional therapeutic agent that is other than a Chromane-Substituted Tetracyclic Compound, wherein the amounts administered are together effective to treat or
15 prevent a viral infection.

 When administering a combination therapy of the invention to a patient, therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The
20 amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a Chromane-Substituted Tetracyclic Compound and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (*e.g.*, a capsule, a tablet and the like).

25 In one embodiment, the at least one Chromane-Substituted Tetracyclic Compound is administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

 In another embodiment, the at least one Chromane-Substituted Tetracyclic Compound and the additional therapeutic agent(s) are administered in
30 doses commonly employed when such agents are used as monotherapy for treating a viral infection.

 In another embodiment, the at least one Chromane-Substituted Tetracyclic Compound and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as
35 monotherapy for treating a viral infection.

 In still another embodiment, the at least one Chromane-Substituted Tetracyclic Compound and the additional therapeutic agent(s) act synergistically and

- 5 are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In one embodiment, the at least one Chromane-Substituted Tetracyclic Compound and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration.

- 10 In another embodiment, this composition is suitable for intravenous administration. In another embodiment, this composition is suitable for subcutaneous administration. In still another embodiment, this composition is suitable for parenteral administration.

Viral infections and virus-related disorders that can be treated or prevented using the combination therapy methods of the present invention include,

- 15 but are not limited to, those listed above.

In one embodiment, the viral infection is HCV infection.

- The at least one Chromane-Substituted Tetracyclic Compound and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of therapy without reducing the efficacy of therapy.

- 20 In one embodiment, the administration of at least one Chromane-Substituted Tetracyclic Compound and the additional therapeutic agent(s) may inhibit the resistance of a viral infection to these agents.

- Non-limiting examples of additional therapeutic agents useful in the present compositions and methods include an interferon, an immunomodulator, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral polymerase inhibitor, a nucleoside inhibitor, a viral protease inhibitor, a viral helicase inhibitor, a virion production inhibitor, a viral entry inhibitor, a viral assembly inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an RNA-dependent polymerase-related disorder.

In one embodiment, the additional therapeutic agent is a viral protease inhibitor.

- 35 In another embodiment, the additional therapeutic agent is a viral replication inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS3 protease inhibitor.

5 In still another embodiment, the additional therapeutic agent is an HCV NS5B polymerase inhibitor.

 In another embodiment, the additional therapeutic agent is a nucleoside inhibitor.

 In another embodiment, the additional therapeutic agent is an
10 interferon.

 In yet another embodiment, the additional therapeutic agent is an HCV replicase inhibitor.

 In another embodiment, the additional therapeutic agent is an antisense agent.

15 In another embodiment, the additional therapeutic agent is a therapeutic vaccine.

 In a further embodiment, the additional therapeutic agent is a virion production inhibitor.

 In another embodiment, the additional therapeutic agent is an antibody
20 therapy.

 In another embodiment, the additional therapeutic agent is an HCV NS2 inhibitor.

 In still another embodiment, the additional therapeutic agent is an HCV NS4A inhibitor.

25 In another embodiment, the additional therapeutic agent is an HCV NS4B inhibitor.

 In another embodiment, the additional therapeutic agent is an HCV NS5A inhibitor

 In yet another embodiment, the additional therapeutic agent is an HCV
30 NS3 helicase inhibitor.

 In another embodiment, the additional therapeutic agent is an HCV IRES inhibitor.

 In another embodiment, the additional therapeutic agent is an HCV p7 inhibitor.

35 In a further embodiment, the additional therapeutic agent is an HCV entry inhibitor.

 In another embodiment, the additional therapeutic agent is an HCV assembly inhibitor.

5 In one embodiment, the additional therapeutic agents comprise a viral protease inhibitor and a viral polymerase inhibitor.

 In still another embodiment, the additional therapeutic agents comprise a viral protease inhibitor and an immunomodulatory agent.

 In yet another embodiment, the additional therapeutic agents comprise
10 a polymerase inhibitor and an immunomodulatory agent.

 In another embodiment, the additional therapeutic agents comprise a viral protease inhibitor and a nucleoside.

 In another embodiment, the additional therapeutic agents comprise an immunomodulatory agent and a nucleoside.

15 In one embodiment, the additional therapeutic agents comprise an HCV protease inhibitor and an HCV polymerase inhibitor.

 In another embodiment, the additional therapeutic agents comprise a nucleoside and an HCV NS5A inhibitor.

 In another embodiment, the additional therapeutic agents comprise a
20 viral protease inhibitor, an immunomodulatory agent and a nucleoside.

 In a further embodiment, the additional therapeutic agents comprise a viral protease inhibitor, a viral polymerase inhibitor and an immunomodulatory agent.

 In another embodiment, the additional therapeutic agent is ribavirin.

 HCV polymerase inhibitors useful in the present compositions and
25 methods include, but are not limited to, VP-19744 (Wyeth/ViroPharma), PSI-7851 (Pharmasset), GS-7977 (sofosbuvir, Gilead), R7128 (Roche/Pharmasset), PF-868554/filibuvir (Pfizer), VCH-759 (ViroChem Pharma), HCV-796 (Wyeth/ViroPharma), IDX-184 (Idenix), IDX-375 (Idenix), NM-283 (Idenix/Novartis), R-1626 (Roche), MK-0608 (Ionis/Merck & Co., Inc., Kenilworth,
30 New Jersey, U.S.A.), INX-8014 (Inhibitex), INX-8018 (Inhibitex), INX-189 (Inhibitex), GS 9190 (Gilead), A-848837 (Abbott), ABT-333 (Abbott), ABT-072 (Abbott), A-837093 (Abbott), BI-207127 (Boehringer-Ingelheim), BILB-1941 (Boehringer-Ingelheim), MK-3281 (Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.), VCH222 (ViroChem), VCH916 (ViroChem), VCH716(ViroChem), GSK-
35 71185 (Glaxo SmithKline), ANA598 (Anadys), GSK-625433 (Glaxo SmithKline), XTL-2125 (XTL Biopharmaceuticals), and those disclosed in Ni *et al.*, *Current Opinion in Drug Discovery and Development*, 7(4):446 (2004); Tan *et al.*, *Nature*

- 5 *Reviews*, 1:867 (2002); and Beaulieu *et al.*, *Current Opinion in Investigational Drugs*, 5:838 (2004).

Other HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in International Publication Nos. WO 08/082484, WO 08/082488, WO 08/083351, WO 08/136815,
10 WO 09/032116, WO 09/032123, WO 09/032124 and WO 09/032125.

Interferons useful in the present compositions and methods include, but are not limited to, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1 and PEG-interferon alpha conjugates. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha
15 conjugates include interferon alpha-2a (RoferonTM, Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (*e.g.*, as sold under the trade name PegasysTM), interferon alpha-2b (IntronTM, Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.) in the form of pegylated interferon alpha-2b (*e.g.*, as sold under the trade name PEG-IntronTM from Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.),
20 interferon alpha-2b-XL (*e.g.*, as sold under the trade name PEG-IntronTM), interferon alpha-2c (Berofer AlphaTM, Boehringer Ingelheim, Ingelheim, Germany), PEG-interferon lambda (Bristol-Myers Squibb and ZymoGenetics), interferon alfa-2b alpha fusion polypeptides, interferon fused with the human blood protein albumin (AlbuferonTM, Human Genome Sciences), Omega Interferon (Intarcia), Locteron
25 controlled release interferon (Biolex/OctoPlus), Biomed-510 (omega interferon), Peg-IL-29 (ZymoGenetics), Locteron CR (Octoplus), IFN- α -2b-XL (Flamel Technologies), and consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (InfergenTM, Amgen, Thousand Oaks, California).

30 Antibody therapy agents useful in the present compositions and methods include, but are not limited to, antibodies specific to IL-10 (such as those disclosed in US Patent Publication No. US2005/0101770, humanized 12G8, a humanized monoclonal antibody against human IL-10, plasmids containing the nucleic acids encoding the humanized 12G8 light and heavy chains were deposited
35 with the American Type Culture Collection (ATCC) as deposit numbers PTA-5923 and PTA-5922, respectively), and the like).

Examples of viral protease inhibitors useful in the present compositions and methods include, but are not limited to, an HCV protease inhibitor.

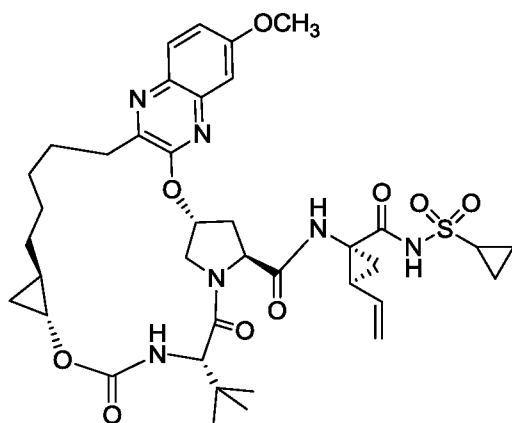
5 HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Nos. 7,494,988, 7,485,625, 7,449,447, 7,442,695, 7,425,576, 7,342,041, 7,253,160, 7,244,721, 7,205,330, 7,192,957, 7,186,747, 7,173,057, 7,169,760, 7,012,066, 6,914,122, 6,911,428, 6,894,072, 6,846,802, 6,838,475, 6,800,434, 6,767,991, 5,017,380, 10 4,933,443, 4,812,561 and 4,634,697; U.S. Patent Publication Nos. US20020068702, US20020160962, US20050119168, US20050176648, US20050209164, US20050249702 and US20070042968; and International Publication Nos. WO 03/006490, WO 03/087092, WO 04/092161 and WO 08/124148.

Additional HCV protease inhibitors useful in the present compositions 15 and methods include, but are not limited to, SCH503034 (Boceprevir, Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.), SCH900518 (Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.), VX-950 (Telaprevir, Vertex), VX-500 (Vertex), VX-813 (Vertex), VBY-376 (Virobay), BI-201335 (Boehringer Ingelheim), TMC-435 (Medivir/Tibotec), ABT-450 (Abbott), TMC-435350 (Medivir), ITMN-191/R7227 20 (InterMune/Roche), EA-058 (Abbott/Enanta), EA-063 (Abbott/Enanta), GS-9132 (Gilead/Achillion), ACH-1095 (Gilead/Achillion), IDX-136 (Idenix), IDX-316 (Idenix), ITMN-8356 (InterMune), ITMN-8347 (InterMune), ITMN-8096 (InterMune), ITMN-7587 (InterMune), BMS-650032 (Bristol-Myers Squibb), VX-985 (Vertex) and PHX1766 (Phenomix).

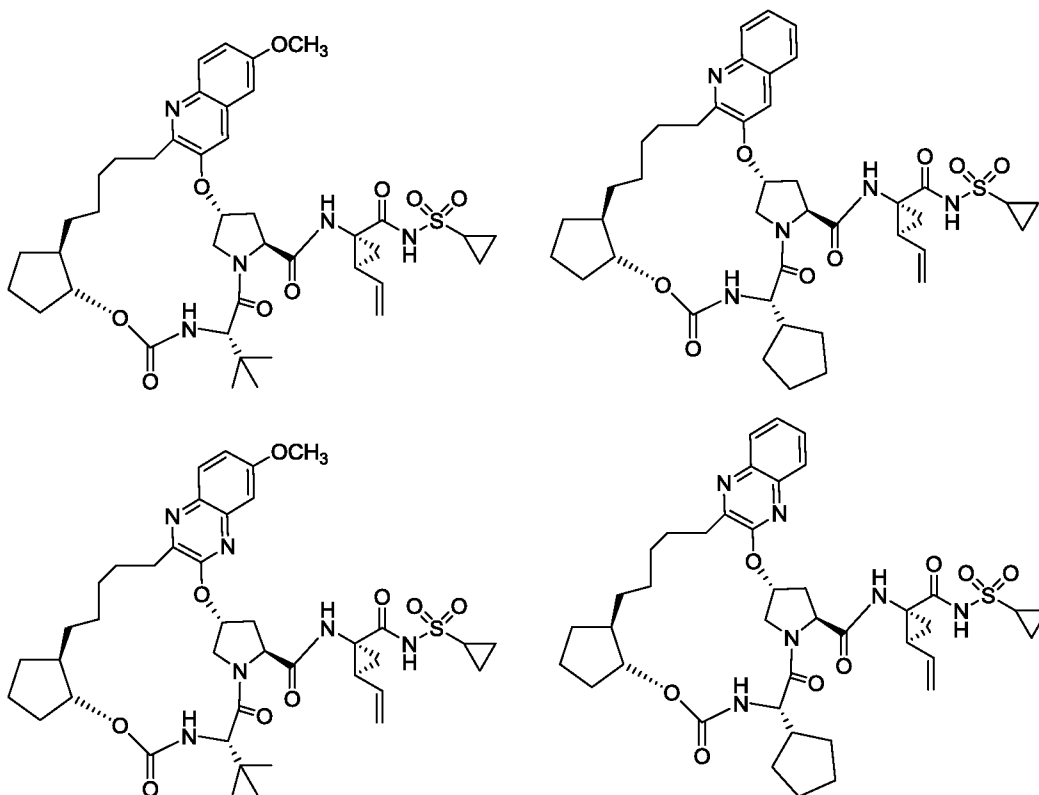
25 Further examples of HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in Landro *et al.*, *Biochemistry*, 36(31):9340-9348 (1997); Ingallinella *et al.*, *Biochemistry*, 37(25):8906-8914 (1998); Llinàs-Brunet *et al.*, *Bioorg Med Chem Lett*, 8(13):1713-1718 (1998); Martin *et al.*, *Biochemistry*, 37(33):11459-11468 (1998); Dimasi *et al.*, *J Virol*, 71(10):7461-7469 (1997); Martin *et al.*, *Protein Eng*, 10(5):607-614 (1997); 30 Elzouki *et al.*, *J Hepat*, 27(1):42-48 (1997); *BioWorld Today*, 9(217):4 (November 10, 1998); U.S. Patent Publication Nos. US2005/0249702 and US 2007/0274951; and International Publication Nos. WO 98/14181, WO 98/17679, WO 98/17679, WO 98/22496 and WO 99/07734 and WO 05/087731.

35 Further examples of HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, grazoprevir (Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.), which has the following structure:

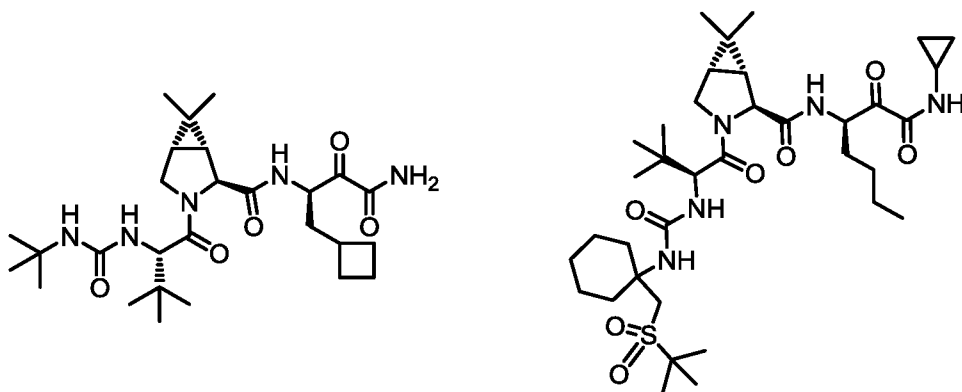
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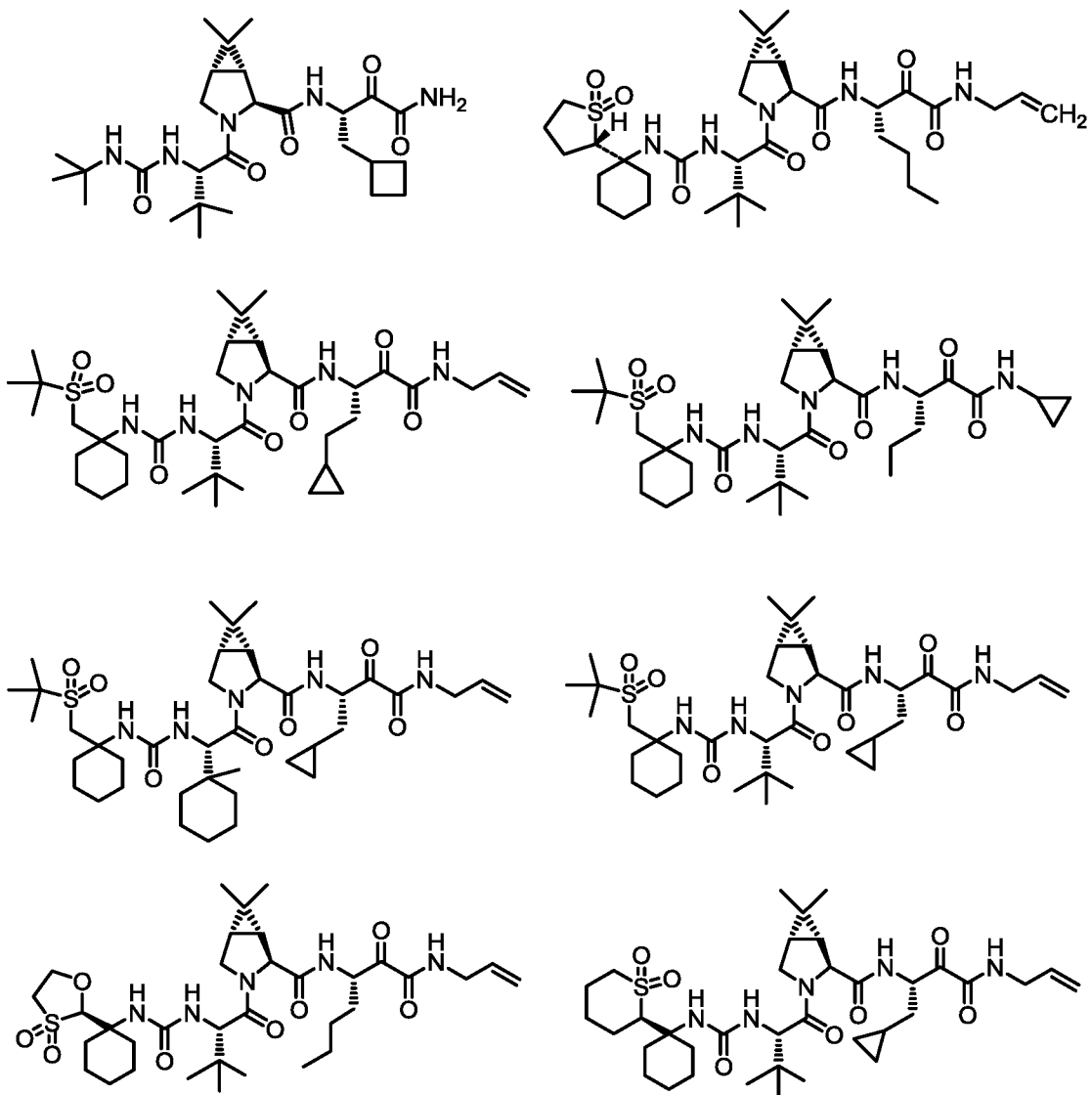
and the following compounds:

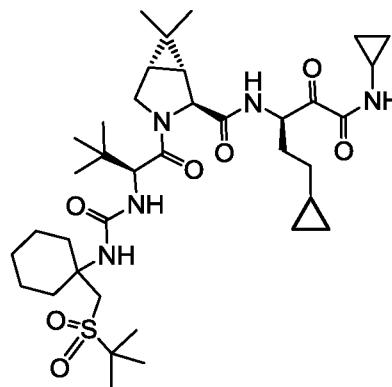
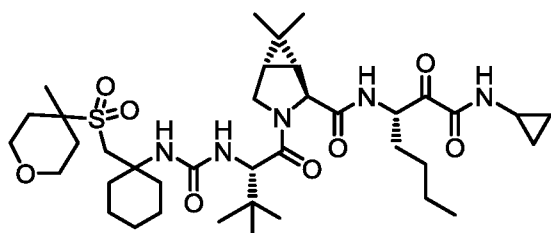
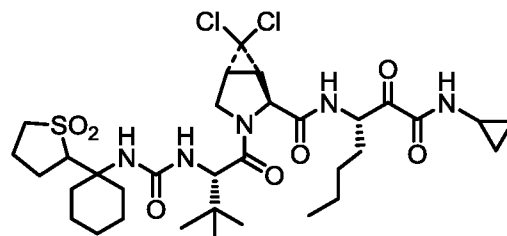
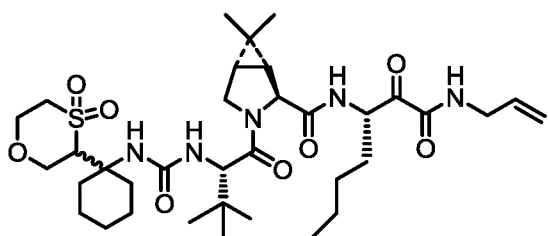


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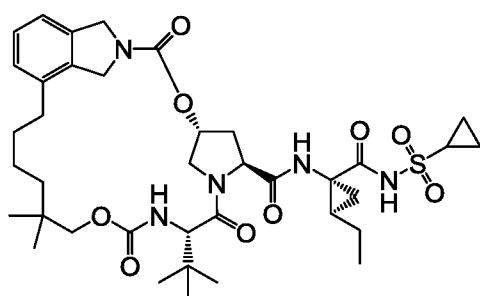
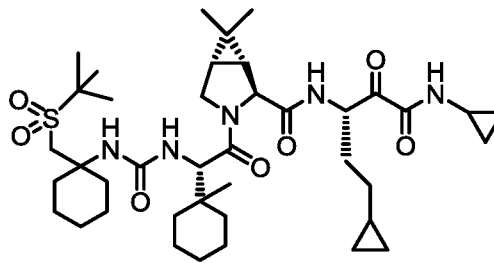
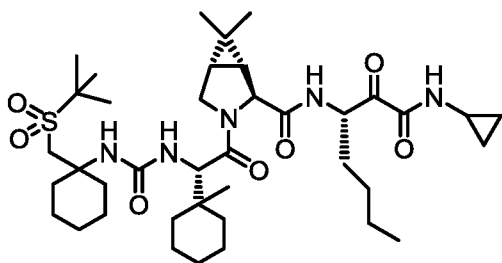
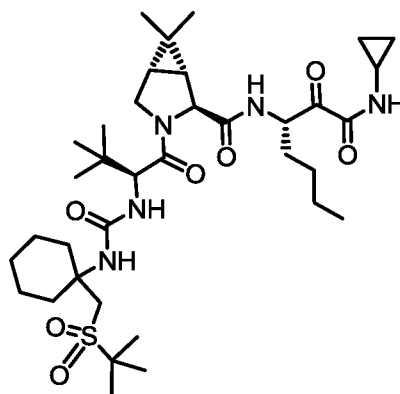
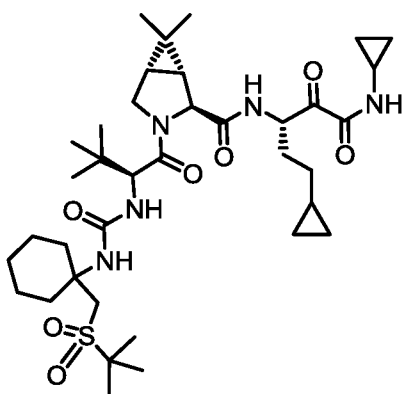


5





5



and

5 HCV viral replication inhibitors useful in the present compositions and methods include, but are not limited to, HCV replicase inhibitors, IRES inhibitors, NS4A inhibitors, NS3 helicase inhibitors, NS3 protease inhibitors, NS5A inhibitors, NS5B inhibitors, ribavirin, AZD-2836 (Astra Zeneca), BMS-790052 (Bristol-Myers Squibb, see Gao *et al.*, *Nature*, 465:96-100 (2010)), viramidine, A-831 (Arrow
10 Therapeutics); an antisense agent or a therapeutic vaccine.

HCV NS4A inhibitors useful in the useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Nos. 7,476,686 and 7,273,885; U.S. Patent Publication No. US20090022688; and International Publication Nos. WO 2006/019831 and WO 2006/019832. Additional
15 HCV NS4A inhibitors useful in the useful in the present compositions and methods include, but are not limited to, AZD2836 (Astra Zeneca) and ACH-806 (Achillon Pharmaceuticals, New Haven, CT).

HCV replicase inhibitors useful in the useful in the present compositions and methods include, but are not limited to, those disclosed in U.S.
20 Patent Publication No. US20090081636.

Therapeutic vaccines useful in the present compositions and methods include, but are not limited to, IC41 (Intercell Novartis), CSL123 (Chiron/CSL), GI 5005 (Globeimmune), TG-4040 (Transgene), GNI-103 (GENimmune), Hepavaxx C (ViRex Medical), ChronVac-C (Inovio/Tripep), PeviPRO™ (Pevion Biotect),
25 HCV/MF59 (Chiron/Novartis) and Civacir (NABI).

Examples of further additional therapeutic agents useful in the present compositions and methods include, but are not limited to, Ritonavir (Abbott), TT033 (Benitec/Tacere Bio/Pfizer), Sirna-034 (Sirna Therapeutics), GNI-104 (GENimmune), GI-5005 (GlobeImmune), IDX-102 (Idenix), Levovirin™ (ICN Pharmaceuticals,
30 Costa Mesa, California); Humax (Genmab), ITX-2155 (Ithrex/Novartis), PRO 206 (Progenics), HepaCide-I (NanoVirocides), MX3235 (Migenix), SCY-635 (Scynexis); KPE02003002 (Kemin Pharma), Lenocta (VioQuest Pharmaceuticals), IET – Interferon Enhancing Therapy (Transition Therapeutics), Zadaxin (SciClone Pharma), VP 50406™ (Viropharma, Incorporated, Exton, Pennsylvania); Taribavirin (Valeant
35 Pharmaceuticals); Nitazoxanide (Romark); Debio 025 (Debiopharm); GS-9450 (Gilead); PF-4878691 (Pfizer); ANA773 (Anadys); SCV-07 (SciClone Pharmaceuticals); NIM-881 (Novartis); Ionis 14803™ (Ionis Pharmaceuticals, Carlsbad, California); Heptazyme™ (Ribozyne Pharmaceuticals, Boulder, Colorado);

5 ThymosinTM (SciClone Pharmaceuticals, San Mateo, California); MaxamineTM (Maxim Pharmaceuticals, San Diego, California); NKB-122 (JenKen Bioscience Inc., North Carolina); Alinia (Romark Laboratories), INFORM-1 (a combination of R7128 and ITMN-191); and mycophenolate mofetil (Hoffman-LaRoche, Nutley, New Jersey).

10 The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of HCV infection can be determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; and the type and severity of the viral infection or related disease
15 or disorder. When administered in combination, the Chromane-Substituted Tetracyclic Compound(s) and the other agent(s) can be administered simultaneously (*i.e.*, in the same composition or in separate compositions one right after the other) or sequentially. This particularly useful when the components of the combination are given on different dosing schedules, *e.g.*, one component is administered once daily
20 and another component is administered every six hours, or when the preferred pharmaceutical compositions are different, *e.g.*, one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

In a further embodiment, when the additional therapeutic agent is Ribavirin (commercially available as REBETOL ribavirin from Merck & Co., Inc.,
25 Kenilworth, New Jersey, U.S.A. or COPEGUS ribavirin from Hoffmann-La Roche), this agent is administered at a daily dosage of from about 600 to about 1400 mg/day for at least 24 weeks.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from: an
30 immunomodulator, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral polymerase inhibitor, a nucleoside inhibitor, a viral protease inhibitor, a viral helicase inhibitor, a viral polymerase inhibitor a virion production inhibitor, a viral entry inhibitor, a viral assembly inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an RNA-dependent polymerase-related
35 disorder.

In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV replication

5 inhibitor, a nucleoside and ribavirin. The combination therapies can include any combination of these additional therapeutic agents.

In another embodiment, one or more compounds of the present invention are administered with one additional therapeutic agent selected from an HCV protease inhibitor and ribavirin.

10 In still another embodiment, one or more compounds of the present invention are administered with two additional therapeutic agents selected from an HCV protease inhibitor, an HCV replication inhibitor, a nucleoside and ribavirin.

In another embodiment, one or more compounds of the present invention are administered with an HCV protease inhibitor and ribavirin. In another
15 specific embodiment, one or more compounds of the present invention are administered with ribavirin.

In another embodiment, one or more compounds of the present invention are administered with three additional therapeutic agents selected from an HCV protease inhibitor, an HCV replication inhibitor, a nucleoside, a pegylated
20 interferon and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are
25 administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, and ribavirin.

30 In one embodiment, one or more compounds of the present invention are administered with one additional therapeutic agent selected from an HCV polymerase inhibitor, a viral protease inhibitor, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with ribavirin.

35 In one embodiment, one or more compounds of the present invention are administered with two additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, and a viral replication inhibitor.

5 In another embodiment, one or more compounds of the present invention are administered with ribavirin and another therapeutic agent.

 In another embodiment, one or more compounds of the present invention are administered with ribavirin and another therapeutic agent, wherein the additional therapeutic agent is selected from an HCV polymerase inhibitor, a viral
10 protease inhibitor, and a viral replication inhibitor.

 In still another embodiment, one or more compounds of the present invention are administered with ribavirin and a viral protease inhibitor.

 In another embodiment, one or more compounds of the present invention are administered with ribavirin and an HCV protease inhibitor.

15 In another embodiment, one or more compounds of the present invention are administered with ribavirin and either boceprevir or telaprevir.

 In a further embodiment, one or more compounds of the present invention are administered with ribavirin and an HCV polymerase inhibitor.

 In another embodiment, one or more compounds of the present
20 invention are administered with ribavirin.

 In one embodiment, one or more compounds of the present invention are administered with grazoprevir.

 In one embodiment, one or more compounds of the present invention are administered with sofosbuvir.

25

Compositions and Administration

 Due to their activity, the Chromane-Substituted Tetracyclic Compounds are useful in veterinary and human medicine. As described above, the Chromane-Substituted Tetracyclic Compounds are useful for treating or preventing
30 HCV infection in a patient in need thereof.

 When administered to a patient, the Chromane-Substituted Tetracyclic Compounds can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one
35 Chromane-Substituted Tetracyclic Compound and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, *i.e.*,

5 oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as
10 lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 0.5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules can be used as
15 solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene
20 glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

25 Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

30 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Additionally, the compositions of the present invention may be
35 formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize therapeutic effects, *i.e.*, antiviral activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release

- 5 polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more Chromane-Substituted Tetracyclic Compounds are administered orally.

- In another embodiment, the one or more Chromane-Substituted
10 Tetracyclic Compounds are administered intravenously.

In still another embodiment, the one or more Chromane-Substituted Tetracyclic Compounds are administered sublingually.

- In one embodiment, a pharmaceutical preparation comprising a Chromane-Substituted Tetracyclic Compound is in unit dosage form. In such form,
15 the preparation is subdivided into unit doses containing effective amounts of the active components.

- Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the Chromane-
20 Substituted Tetracyclic Compound(s) by weight or volume. In various embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the Chromane-Substituted Tetracyclic Compound(s) by weight or volume.

- The amount and frequency of administration of the Chromane-
25 Substituted Tetracyclic Compounds will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. Generally, a total daily dosage of the at least one Chromane-Substituted Tetracyclic Compound(s) alone, or when administered as combination therapy, can range from about 1 to about 2500 mg per
30 day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one embodiment, the dosage is from about 10 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from
35 about 1 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 500 to about 1500 mg/day, administered in a single dose or in 2-4 divided doses.

5 In still another embodiment, the dosage is from about 500 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 100 to about 500 mg/day, administered in a single dose or in 2-4 divided doses.

The compositions of the invention can further comprise one or more
10 additional therapeutic agents, selected from those listed above herein. Accordingly, in one embodiment, the present invention provides compositions comprising: (i) at least one Chromane-Substituted Tetracyclic Compound or a pharmaceutically acceptable salt thereof; (ii) one or more additional therapeutic agents that are not a Chromane-Substituted Tetracyclic Compound; and (iii) a pharmaceutically acceptable carrier,
15 wherein the amounts in the composition are together effective to treat HCV infection.

In one embodiment, the present invention provides compositions comprising a Compound of Formula (I) and a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides compositions comprising a Compound of Formula (I), a pharmaceutically acceptable carrier, and a
20 second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

In another embodiment, the present invention provides compositions comprising a Compound of Formula (I), a pharmaceutically acceptable carrier, and two additional therapeutic agents, each of which are independently selected from the
25 group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

Kits

In one aspect, the present invention provides a kit comprising a
30 therapeutically effective amount of at least one Chromane-Substituted Tetracyclic Compound, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

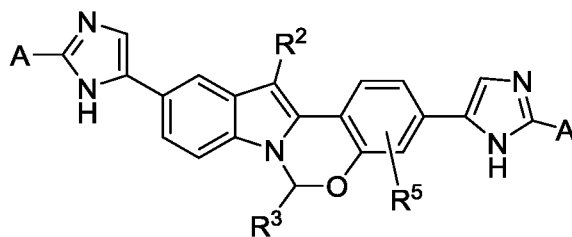
In another aspect the present invention provides a kit comprising an amount of at least one Chromane-Substituted Tetracyclic Compound, or a
35 pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more active ingredients result in a desired therapeutic effect. In one embodiment, the one or more Chromane-Substituted Tetracyclic Compounds and the

- 5 one or more additional therapeutic agents are provided in the same container. In one embodiment, the one or more Chromane-Substituted Tetracyclic Compounds and the one or more additional therapeutic agents are provided in separate containers.

5

CLAIMS

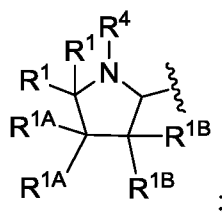
1. A compound having the formula (I):



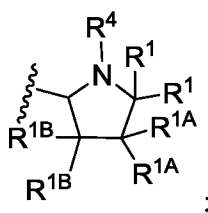
(I)

- 10 or a pharmaceutically acceptable salt thereof, wherein:

A is:



A' is:



- 15 each occurrence of R^1 is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkyl, $-O$ - C_1 - C_6 alkyl, $-N(R^9)_2$, $-O$ -(C_1 - C_6 haloalkyl), and halo;

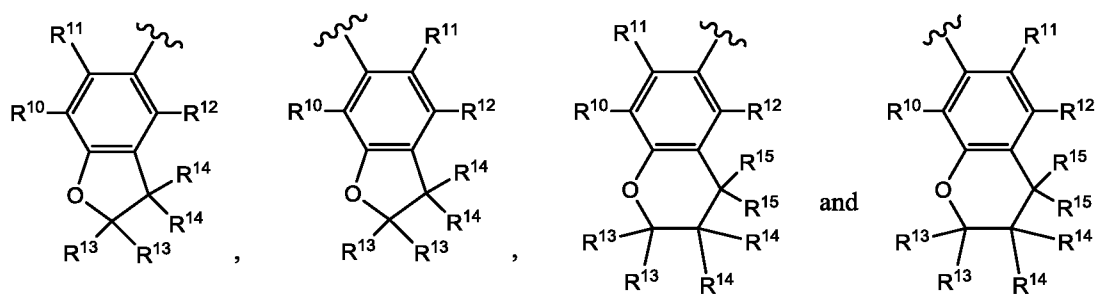
- each occurrence of R^{1A} is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkyl, $-O$ - C_1 - C_6 alkyl, $-N(R^9)_2$, $-O$ -(C_1 - C_6 haloalkyl), and halo, or one R^{1A} group and an R^1 group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused C_3 - C_7 cycloalkyl group, or two R^{1A} groups that are attached to the same carbon atom, and the common carbon atom to which they are attached, can combine to form a spirocyclic C_3 - C_7 cycloalkyl group;

- 25 each occurrence of R^{1B} is independently selected from H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkyl, $-O$ - C_1 - C_6 alkyl, $-N(R^9)_2$, $-O$ -(C_1 - C_6 haloalkyl) and halo, or an R^{1B} group and an R^{1A} group that are attached to the same ring,

- 5 together with the carbon atoms to which they are attached, can combine to form a fused C₃-C₇ cycloalkyl group, or an R^{1B} group and an R¹ group that are attached to the same ring, can combine to form a bridging group having the formula -CH₂- or -CH₂CH₂-;

R² is selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and halo;

- 10 R³ is selected from:



each occurrence of R⁴ is independently selected from -C(O)-C(R⁷)₂NHC(O)O-R⁸ and -C(O)-C(R⁷)₂-N(R⁶)₂

- R⁵ represents up to 3 optional substituents, each independently selected from halo, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₇ cycloalkyl, 4 to 6-membered monocyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, C₆-C₁₀ aryl, benzyl and -O-(C₁-C₆ alkyl), wherein said C₃-C₇ cycloalkyl group, said 4 to 6-membered monocyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group, said C₆-C₁₀ aryl group, or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -O-C₁-C₆ alkyl, -(C₁-C₆ alkylene)-O-C₁-C₆ alkyl and -O-(C₁-C₆ haloalkyl);

- each occurrence of R⁶ is independently selected from H, C₁-C₆ alkyl and C₃-C₇ cycloalkyl, wherein two R⁶ groups, together with the nitrogen atom to which they are attached, can combine to form a 4 to 8-membered monocyclic heterocycloalkyl;

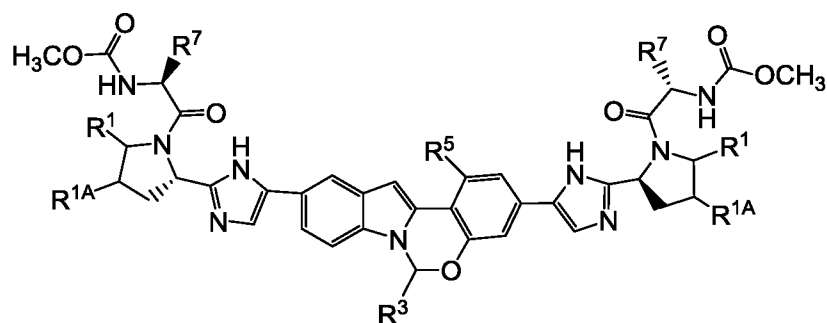
- each occurrence of R⁷ is independently selected from H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl, 4 to 8-membered monocyclic heterocycloalkyl, 6 to 10-membered bicyclic heterocycloalkyl and C₃-C₇ cycloalkyl, wherein said 4 to 8-membered monocyclic heterocycloalkyl group, said 6 to 10-membered bicyclic heterocycloalkyl group and said C₃-C₇ cycloalkyl group can be optionally substituted with up to 5 groups, each independently selected from halo, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₇ cycloalkyl, -O-C₁-C₆ alkyl, -N(R⁹)₂ and -O-(C₁-C₆ haloalkyl), and

- 5 wherein said C₃-C₇ cycloalkyl group can be optionally fused to a 4 to 6-membered monocyclic heterocycloalkyl group, and wherein said 4 to 8-membered monocyclic heterocycloalkyl group and said C₃-C₇ cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic C₃-C₆ cycloalkyl group; and wherein said C₃-C₇ cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic 3 to 6-
- 10 membered monocyclic heterocycloalkyl group, and wherein two R⁷ groups, that are attached to a common carbon atom, together with the common carbon atom to which they are attached, can combine to form a spirocyclic C₃-C₇ cycloalkyl group;
- each occurrence of R⁸ is independently selected from C₁-C₆ alkyl, C₃-C₇ cycloalkyl and C₆-C₁₀ aryl;
- 15 each occurrence of R⁹ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and C₆-C₁₀ aryl;
- R¹⁰ is selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo;
- R¹¹ is selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo;
- R¹² is selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo;
- 20 each occurrence of R¹³ is independently selected from H, C₁-C₆ alkyl and C₃-C₇ cycloalkyl, or both R¹³ groups and the common carbon atom to which they are each attached, can combine to form a spirocyclic C₃-C₇ cycloalkyl group;
- each occurrence of R¹⁴ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo; or both R¹⁴ groups and the common carbon atom to which
- 25 they are each attached, join to form a spirocyclic C₃-C₇ cycloalkyl group; or an R¹⁴ group and R¹³ group, together with the carbon atoms to which they are each attached, join to form a fused C₃-C₇ cycloalkyl group; or an R¹⁴ group and R¹⁵ group, together with the carbon atoms to which they are each attached, can combine to form a fused C₃-C₇ cycloalkyl group; and
- 30 each occurrence of R¹⁵ is independently selected from H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl and halo, or both R¹⁵ groups and the common carbon atom to which they are each attached, can combine to form a spirocyclic C₃-C₇ cycloalkyl group.

2. The compound of claim 1, wherein each occurrence of
- 35 R⁴ is independently -C(O)CH(R⁷)NHC(O)OCH₃, or a pharmaceutically acceptable salt thereof.

5 3. The compound of claim 2, wherein R⁷ is selected from C₁-C₆
alkyl, C₁-C₆ haloalkyl and 4 to 6-membered monocyclic heterocycloalkyl, wherein
said 4 to 6-membered monocyclic heterocycloalkyl group can be optionally
substituted with up to five C₁-C₆ alkyl groups or said 4 to 6-membered monocyclic
heterocycloalkyl group can be optionally substituted on a ring carbon atom with a
10 spirocyclic C₃-C₆ cycloalkyl group, or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1 having the formula:



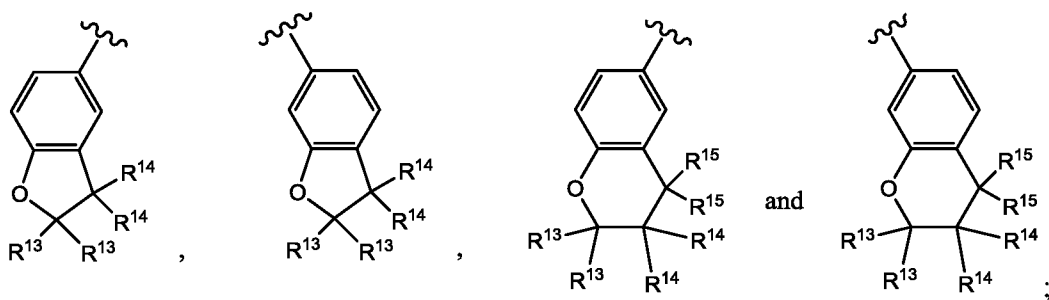
(Ia)

or a pharmaceutically acceptable salt thereof,
wherein:

each R^1 is H ;

each R^{1A} is independently H or F, or an R^{1A} group and an R¹ group that
20 are attached to same ring, together with the ring carbon atoms to which they are
attached, can combine to form a fused cyclopropyl group;

R^3 is selected from:



R⁵ is H, F or methyl;

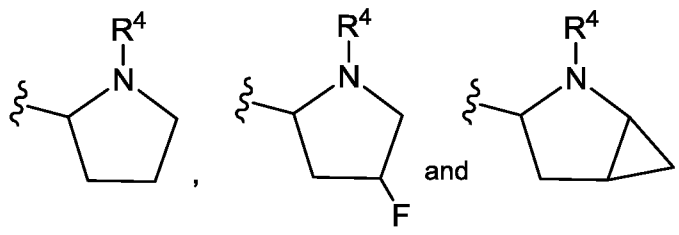
25 each occurrence of R⁷ is independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl and 4 to 6-membered monocyclic heterocycloalkyl, wherein said 4 to 6- membered monocyclic heterocycloalkyl group can be optionally substituted with up to 2 groups, each independently selected from C₁-C₆ alkyl;

5 each occurrence of R^{13} is independently selected from H and C_1 - C_6 alkyl, or both R^{13} groups and the common carbon atom to which they are each attached, join to form a spirocyclic C_3 - C_7 cycloalkyl group;

each occurrence of R^{14} is independently selected from H, halo and C_1 - C_6 alkyl; or both R^{14} groups and the common carbon atom to which they are each attached, join to form a spirocyclic C_3 - C_7 cycloalkyl group; or an R^{14} group and R^{13} group, together with the carbon atoms to which they are each attached, join to form a fused C_3 - C_7 cycloalkyl group; or an R^{14} group and R^{15} group, together with the carbon atoms to which they are each attached, join to form a fused C_3 - C_7 cycloalkyl group; and

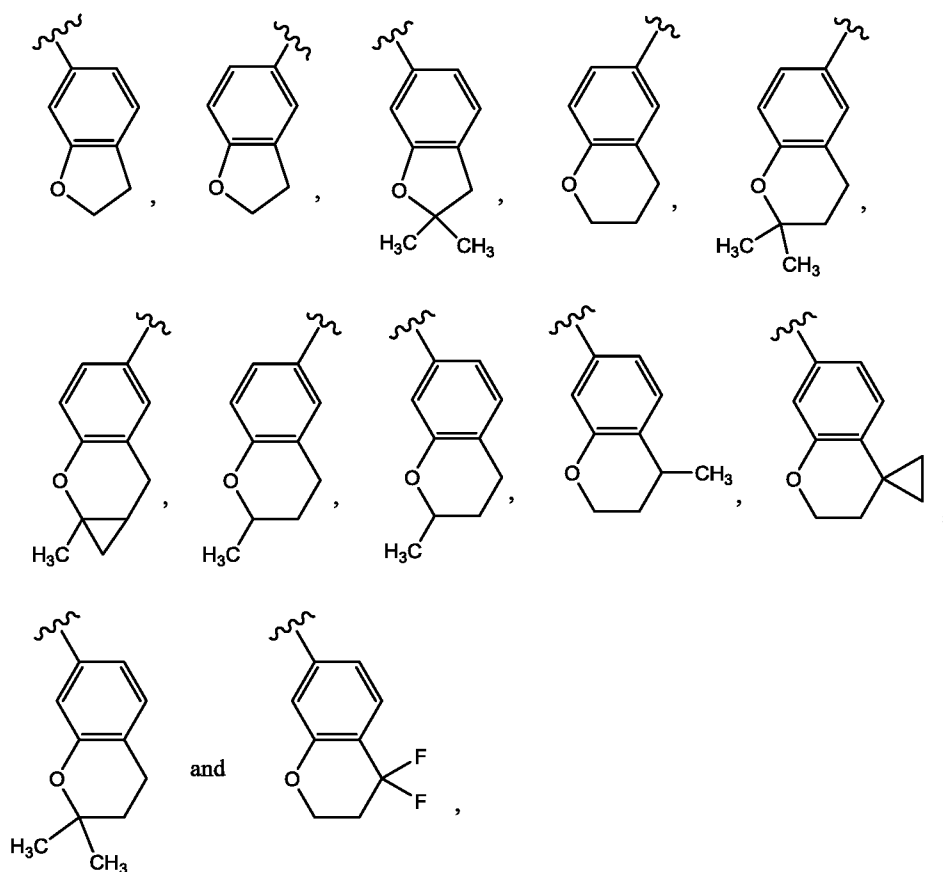
15 each occurrence of R^{15} is independently selected from H, C_1 - C_6 alkyl and halo, or both R^{15} groups and the common carbon atom to which they are each attached, join to form a spirocyclic C_3 - C_7 cycloalkyl group.

5. The compound of any one of claims 1 to 4, wherein A and A' are each independently selected from:



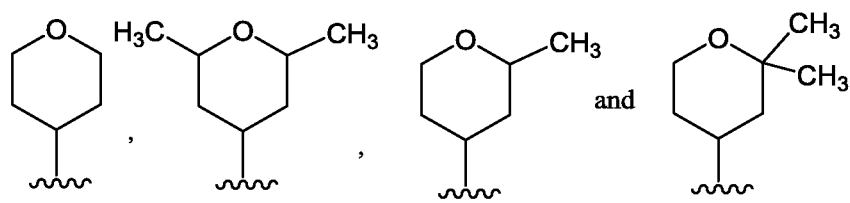
or a pharmaceutically acceptable salt thereof.

6. The compound of claim any of claims 1 to 5, wherein R^3 is selected from:



or a pharmaceutically acceptable salt thereof.

7. The compound of any of claims 1 to 6, wherein each occurrence of R^7 is independently selected from isopropyl, $-\text{CF}(\text{CH}_3)_2$,
 10 $-\text{CH}(\text{CH}_3)\text{OCH}_2\text{CH}_3$,



or a pharmaceutically acceptable salt thereof.

8. A compound selected from any of the compounds numbered 1-
 15 94 in the above specification, or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising an effective amount of the compound of any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5

10. The pharmaceutical composition according to claim 9 further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

10

11. The pharmaceutical composition according to claim 10, further comprising a third therapeutic agent selected from the group consisting of HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

15

12. The use of the composition according to any of claims 9 to 11 for inhibiting HCV replication or for treating infection by HCV in a patient in need thereof.

20

13. A method of treating a patient infected with HCV comprising the step of administering an amount of the compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, effective to treat infection by HCV in said patient.

25

14. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in (i) the inhibition of HCV replication or (ii) the treatment of infection by HCV, in a patient in need thereof.

30

15. The method according to claim 13, further comprising administering a second additional therapeutic agent to said patient, wherein said second additional therapeutic agent is independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

35

16. The method according to claim 15, further comprising administering a third additional therapeutic agent to said patient, wherein said third additional therapeutic agent is independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

17. The method according to claim 15 or 16, wherein said second additional therapeutic agent is grazoprevir.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/095881

A. CLASSIFICATION OF SUBJECT MATTER

C07D 498/04(2006.01)i; C07D 487/04(2006.01)i; C07D 471/04(2006.01)i; A61K 31/5365(2006.01)i; A61K 31/4985(2006.01)i; A61K 31/437(2006.01)i; A61P 31/14(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI,EPODOC,CNKI,CNPAT,STN,tetracyclic,indole,HCV,hepatitis C virus, NS5A,inhibitor,multicyclic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012041014 A1 (MERCK SHARP & DOHME CORP. ET AL.) 05 April 2012 (2012-04-05) claims 1-22, paragraph 1 in page 1, compounds 357, 358, 426, 1397, 1430 and 1431	1-17
A	WO 2009102568 A1 (BRISTOL- MYERS SQUIBB COMPANY) 20 August 2009 (2009-08-20) abstract, claims 1-25	1-17
A	WO 2010065674 A1 (PRESIDIO PHARMACEUTICALS, INC. ET AL.) 10 June 2010 (2010-06-10) abstract, claims 1-95	1-17

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

03 May 2017

Date of mailing of the international search report

24 May 2017

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/095881

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **12-13, 15-17**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 12-13, 15-17 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. However the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/095881

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2012041014	A1	05 April 2012	EP	2621931	A4	19 March 2014
				KR	20140001879	A	07 January 2014
				CA	2811662	A1	05 April 2012
				JP	2013538831	A	17 October 2013
				MX	2013003631	A	01 October 2013
				AU	2011307953	B2	31 July 2014
				EP	2621931	A1	07 August 2013
				AU	2011307953	A1	04 April 2013
WO	2009102568	A1	20 August 2009	US	2009202483	A1	13 August 2009
				EP	2242750	B1	24 April 2013
				NZ	586990	A	27 April 2012
				AU	2009215105	B2	26 September 2013
				CO	6251260	A2	21 February 2011
				CA	2715550	C	20 September 2016
				EA	020511	B1	28 November 2014
				MX	2010008531	A	30 August 2010
				SI	2242750	T1	30 August 2013
				TW	200938191	A	16 September 2009
				DK	2242750	T3	29 July 2013
				US	7704992	B2	27 April 2010
				CN	101998954	B	03 June 2015
				JP	2011511837	A	14 April 2011
				EA	201001275	A1	30 June 2011
				CN	101998954	A	30 March 2011
				TW	1423798	B	21 January 2014
				ES	2415208	T3	24 July 2013
				PT	2242750	E	28 June 2013
				EP	2242750	A1	27 October 2010
				KR	101614964	B1	22 April 2016
				JP	5425815	B2	26 February 2014
				AU	2009215105	A1	20 August 2009
				ZA	201005485	B	25 January 2012
				HR	P20130421	T1	30 June 2013
				HK	1144195	A1	16 August 2013
				PE	15752009	A1	04 November 2009
				AR	070365	A1	31 March 2010
				CY	1114298	T1	31 August 2016
				KR	20100121651	A	18 November 2010
				CA	2715550	A1	20 August 2009
				IL	207258	D0	30 December 2010
WO	2010065674	A1	10 June 2010	AR	080263	A1	28 March 2012
				EA	024853	B1	31 October 2016
				AU	2009322393	B2	02 February 2017
				HK	1203929	A1	06 November 2015
				EP	2373172	B1	17 July 2013
				CO	6390077	A2	29 February 2012
				SI	2373172	T1	31 December 2013
				US	2012122864	A1	17 May 2012
				US	8618151	B2	31 December 2013
				PT	2373172	E	21 October 2013

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/095881

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		TW 201529569 A	01 August 2015
		DK 2373172 T3	21 October 2013
		CN 104163816 A	26 November 2014
		IL 233818 D0	30 September 2014
		IL 213277 A	31 August 2014
		US 8921369 B2	30 December 2014
		JP 2012510524 A	10 May 2012
		WO 2010065674 A9	31 May 2012
		EP 2373172 A4	01 August 2012
		ES 2437156 T3	09 January 2014
		AU 2009322393 A1	07 July 2011
		US 2013096101 A1	18 April 2013
		KR 20110098780 A	01 September 2011
		MX 2011005898 A	27 September 2011
		TW 201033197 A	16 September 2010
		ZA 201104833 B	28 March 2012
		CN 102647909 B	25 June 2014
		HR P20130944 T1	22 November 2013
		EP 2682393 A1	08 January 2014
		EP 2373172 A1	12 October 2011
		CN 102647909 A	22 August 2012
		EA 201190013 A1	28 February 2012
		TW I480278 B	11 April 2015
		JP 5762971 B2	12 August 2015
		IL 213277 D0	31 July 2011
		CY 1114509 T1	05 October 2016
		PE 09392015 A1	19 July 2015
		SG 171889 A1	28 July 2011
		PE 01242012 A1	17 March 2012
		CA 2746004 A1	10 June 2010