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(54) Titre : PYRIDOPYRAZINEDIONES CYCLOPROPABENZOFURANYLS NOVATEURS
(54) Title: NOVEL CYCLOPROPABENZOFURANYL PYRIDOPYRAZINEDIONES

Formula 1

(57) Abrégé/Abstract:
Compounds and pharmaceutically acceptable salts of the compounds are disclosed, wherein the compounds have the structure of Formula I

(see formula I)

wherein X, R1, R2a, R2b, R3a, R3b, R4a, R4b, R5, R6, R7, R10, R11, and y are as defined in the specification. Corresponding pharmaceutical compositions, potential uses thereof as γ- secrettase modulators, methods of synthesis, and intermediates are also disclosed.
Abstract

Compounds and pharmaceutically acceptable salts of the compounds are disclosed, wherein the compounds have the structure of Formula I

wherein X, R₁, R²a, R²b, R⁴a, R⁴b, R⁵a, R⁵b, R⁶, R⁷, R¹⁰, R¹¹, and y are as defined in the specification. Corresponding pharmaceutical compositions, potential uses thereof as γ-secretase modulators, methods of synthesis, and intermediates are also disclosed.
NOVEL CYCLOPROPABENZOFURANYL PYRIDOPYRAZINEDIONES

FIELD OF THE INVENTION

The present invention relates to novel cyclopropabenzo furanyl pyridopyrazinedione compounds of Formula I, which may be used as γ-secretase modulators.

BACKGROUND OF THE INVENTION

Dementia results from a wide variety of distinctive pathological processes. The most common pathological processes causing dementia are Alzheimer's disease (AD), cerebral amyloid angiopathy (CM) and prion-mediated diseases (see, e.g., Haan et al., Clin. Neurol. Neurosurg. 1990, 92(4):305-310; Glenner et al., J. Neurol. Sci. 1989, 94:1-28). AD affects nearly half of all people past the age of 85, the most rapidly growing portion of the United States population. As such, the number of AD patients in the United States is expected to increase from about 4 million to about 14 million by 2050.

The present invention relates to a group of compounds which may be used as γ-secretase modulators. γ-Secretase modulators may be useful for the treatment of neurodegenerative and/or neurological disorders such as Alzheimer's disease and Down's syndrome. (see Ann. Rep. Med. Chem. 2007, Olsen et al., 42: 27-47).

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula I:

or pharmaceutically acceptable salts thereof, wherein:
X is a (5- to 14-membered) heteroaryl containing 1-3 heteroatoms;

R', where chemically permissible, is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₃-C₆)cycloalkyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴;

R²ₐ and R²ᵇ, where chemically permissible, at each occurrence, are independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or R²ₐ and R²ᵇ together with the carbon atom(s) to which they are attached form a (C₃-C₆)cycloalkyl or a (4- to 10-membered) heterocycloalkyl, wherein the (C₃-C₆)cycloalkyl and the (4- to 10-membered) heterocycloalkyl are optionally substituted with one to three R⁸;

R⁴ₐ and R⁴ᵇ, where chemically permissible, are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or R⁴ₐ and R⁴ᵇ together with the carbon atom to which they are attached form a (C₃-C₆)cycloalkyl, wherein the (C₃-C₆)cycloalkyl is optionally substituted with one to three R⁸;

R⁵ₐ and R⁵ᵇ, at each occurrence, are independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or R⁵ₐ and R⁵ᵇ together with the carbon atom to which they are attached form a (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl is optionally substituted with one to three R⁸.
R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, halogen, cyano, -SF₅, nitro, optionally substituted (C₁−C₆)alkyl, optionally substituted (C₂−C₆)alkenyl, optionally substituted (C₂−C₆)alkynyl, optionally substituted thio(C₁−C₆)alkyl, optionally substituted (C₁−C₆)alkoxy, optionally substituted (C₁−C₆)alkoxy(C₁−C₆)alkyl, optionally substituted (C₃−C₈)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=(O)R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, -C(=O)-OR⁴; and -OR⁵; provided that R⁶ and R⁷ cannot both be hydroxy.

R⁸, at each occurrence, is independently selected from the group consisting of cyano, halogen, hydroxy, -SF₅, nitro, optionally substituted (C₁−C₆)alkyl, optionally substituted (C₁−C₆)alkoxy, and optionally substituted (C₁−C₆)alkoxy(C₁−C₆)alkyl;

R⁹ is selected from the group consisting of hydrogen and optionally substituted (C₁−C₆)alkyl;
y is an integer selected from 1, 2, 3 or 4;

ring B is optionally substituted with one to three R¹⁰, wherein each R¹⁰ is independently selected from the group consisting of halogen, cyano, hydroxy, -SF₅, nitro, optionally substituted (C₁−C₆)alkyl, optionally substituted (C₂−C₆)alkenyl, optionally substituted (C₂−C₆)alkynyl, optionally substituted thio(C₁−C₆)alkyl, optionally substituted (C₁−C₆)alkoxy, optionally substituted (C₃−C₈)cycloalkyl, -N(R⁴)(R⁵), -N(R⁴)(C=(O)R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, -C(=O)-OR⁴; or two R¹⁰ substituents taken together with the carbon atom(s) to which they are attached form an optionally substituted (C₃−C₈)cycloalkyl;

ring D is optionally substituted with one to four R¹¹, wherein each R¹¹ is independently selected from the group consisting of halogen, cyano, hydroxy, -SF₅, nitro, optionally substituted (C₁−C₆)alkyl, optionally substituted (C₂−C₆)alkenyl, optionally substituted (C₂−C₆)alkynyl, optionally substituted thio(C₁−C₆)alkyl, optionally substituted (C₁−C₆)alkoxy, optionally substituted (C₃−C₈)cycloalkyl, optionally substituted (4- to 6-membered)heterocycloalkyl; -N(R⁴)(R⁵), -N(R⁴)(C=(O)R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; and

R³ and R⁵, at each occurrence, are each independently selected from hydrogen or optionally substituted (C₁−C₆)alkyl;

provided that the compound is not 7-(4-methyl-1H-imidazol-1-yl)-2-[[5-(trifluoromethyl)-1,1a-di hydro-6bH-cyclopenta[b][1]benzofuran-6b-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione.

Compounds of the invention include Examples 2-22, C22, C33, C40 and C44 or a pharmaceutically acceptable salt thereof as described herein.
Also provided herein are compositions comprising one or more of the compounds described herein and a pharmaceutically acceptable vehicle, carrier or excipient.

The compounds of Formula I may be used as γ-secretase modulators, and more particularly for reducing the production of amyloid beta (Aβ) protein Aβ 42B. γ-Secretase plays a role in the production of amyloid beta protein (Aβ) plaques associated with Alzheimer’s disease.

Other features and advantages of this invention will be apparent from this specification and the appending claims which describe the invention.

DETAILED DESCRIPTION OF THE INVENTION

The headings within this document are only being utilized to expedite its review by the reader. They should not be construed as limiting the invention or claims in any manner.

Definitions and Exemplifications

As used throughout this application, including the claims, the following terms have the meanings defined below, unless specifically indicated otherwise. The plural and singular should be treated as interchangeable, other than the indication of number:

The term “(C₁-C₆)alkyl” refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from 1 to 6 carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, and hexyl.

The term “optionally substituted (C₁-C₆)alkyl”, as used herein, refers to a (C₁-C₆)alkyl as defined above, in which one or more hydrogen atoms are replaced by a substituent selected from the group consisting of halogen, oxo, cyano, hydroxy, -SF₅, nitro, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -N(R⁴)C(=O)-OR⁵, -C(=O)-N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, -C(=O)-OR⁴, and (C₃-C₆)cycloalkyl, in which R⁴ and R⁵ are each independently hydrogen or optionally substituted (C₁-C₆)alkyl. For example, a (C₁-C₆)alkyl moiety can be substituted with one or more halogen atoms to form a “halo(C₁-C₆)alkyl”. Representative examples of a halo(C₁-C₆)alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, pentafluoroethyl, and the like.

The term “(C₁-C₂)alkyl” refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from 1 to 3 carbon atoms. Examples of such substituents include methyl, ethyl, and propyl (including n-propyl and isopropyl).
The term "(C2-C6)alkenyl" refers to an aliphatic hydrocarbon having from 2 to 6 carbon atoms and having at least one carbon-carbon double bond, including straight chain or branched-chain groups having at least one carbon-carbon double bond. Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl (allyl), isopropenyl, 2-methyl-1-propenyl, 1-butynyl, and 2-butenyl. When the compounds of the invention contain a (C2-C6)alkenyl group, the compound may exist as the pure E (entgegen) form, the pure Z (zusammen) form, or any mixture thereof.

The term "optionally substituted (C2-C6)alkenyl" refers to a (C2-C6)alkenyl as defined above, in which one or more hydrogen atoms are replaced by a substituent selected from the group consisting of halogen, o xo, cyano, hydroxy, -SF5, nitro, -N(R4)(R5), -N(R4)(C(=O)R5), -N(R4)C(=O)OR5, -C(=O)-N(R4)(R5), -O-C(=O)N(R4)(R5), -C(=O)-R4, -C(=O)-OR4, and (C3-C8)cycloalkyl, in which R4 and R5 are each independently hydrogen or optionally substituted (C1-C6)alkyl.

The term "(C2-C6)alkynyl" refers to an aliphatic hydrocarbon having from 2 to 6 carbon atoms and having at least one carbon-carbon triple bond, including straight chain or branched chain groups having at least one carbon-carbon triple bond. Representative examples of an alkynyl include, but are not limited to, acetylenyl, 1-propynyl, 2-propynyl, 3-butylnyl, 2-pentynyl, and 1-butylnyl.

The term "optionally substituted (C2-C6)alkynyl" refers to a (C2-C6)alkynyl as defined above, in which one or more hydrogen atoms are replaced by a substituent selected from the group consisting of halogen, o xo, cyano, hydroxy, -SF5, -N(R4)(R5), -N(R4)(C(=O)R5), -N(R4)C(=O)OR5, -C(=O)-N(R4)(R5), -O-C(=O)N(R4)(R5), -C(=O)-R4, -C(=O)-OR4, and (C3-C8)cycloalkyl, in which R4 and R5 are each independently hydrogen or optionally substituted (C1-C6)alkyl.

The term "halogen" refers to fluorine (which may be depicted as -F), chlorine (which may be depicted as -Cl), bromine (which may be depicted as -Br), or iodine (which may be depicted as -I).

The term "(C1-C6)alkoxy" as used herein, means a (C1-C6)alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom. Examples include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentoxy, and hexyloxy.

The term "optionally substituted (C1-C6)alkoxy" as used herein, refers to a (C1-C6)alkoxy group, as defined above, in which one or more hydrogen atoms are replaced by a substituent selected from the group consisting of halogen, o xo, cyano, hydroxy, -SF5, nitro, -N(R4)(R5), -N(R4)(C(=O)R5), -N(R4)C(=O)OR5, -C(=O)-N(R4)(R5), -O-C(=O)N(R4)(R5), -C(=O)-R4, -C(=O)-OR4, and (C3-C8)cycloalkyl, in which R4 and R5 are each independently hydrogen or optionally substituted (C1-C6)alkyl. For example, a (C1-C6)alkoxy can be
substituted with one or more halogen atoms to form a "halo(C_1-C_6)alkoxy". Representative examples of a halo(C_1-C_6)alkoxy include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy, and pentafluoroethoxy, and the like.

The term "(C_1-C_6)alkoxy(C_1-C_6)alkyl" as used herein, means a (C_1-C_6)alkoxy group, as defined above, attached to the parent moiety through a (C_1-C_6)alkyl group, as defined above. Examples include, but are not limited to, methoxymethyl, methoxyethyl and the like.

The term "optionally substituted (C_1-C_6)alkoxy(C_1-C_6)alkyl" as used herein, means a (C_1-C_6)alkoxy(C_1-C_6)alkyl group, as defined above, in which one or more hydrogen atoms are replaced by a substituent selected from the group consisting of halogen, oxo, cyano, hydroxy, -SF_5, nitro, -N(R^6)(R^5), -N(R^6)(C(O)R^5), -N(R^6)(C(O)=O)OR^5, -C(=O)-N(R^6)(R^5), -O-C(=O)N(R^4)(R^5), -C(=O)-R^4, -C(=O)-OR^4, and (C_3-C_6)cycloalkyl, in which R^4 and R^5 are each independently hydrogen or optionally substituted (C_1-C_6)alkyl.

The term "thio(C_1-C_6)alkyl" as used herein, means a (C_1-C_6)alkyl group, as defined above, appended to the parent molecular moiety through a sulfur atom. Representative examples of thio(C_1-C_6)alkythio include, but are not limited to, thiomethyl, thioethyl, thio(tert-butyl), and thiohexyl.

The term "optionally substituted thio(C_1-C_6)alkyl", as used herein, refers to a thio(C_1-C_6)alkyl group, as defined above, in which one or more hydrogen atoms are replaced by a substituent selected from the group consisting of halogen, oxo, cyano, hydroxy, -SF_5, nitro, -N(R^6)(R^5), -N(R^6)(C(O)R^5), -N(R^6)(C(O)=O)OR^5, -C(=O)-N(R^6)(R^5), -O-C(=O)N(R^4)(R^5), -C(=O)-R^4, -C(=O)-OR^4, and (C_3-C_6)cycloalkyl, in which R^4 and R^5 are each independently hydrogen or optionally substituted (C_1-C_6)alkyl.

The term "(C_3-C_6)cycloalkyl" refers to a carbocyclic substituent obtained by removing a hydrogen from a saturated carbocyclic molecule having from 3 to 8 carbon atoms. A "(C_3-C_6)cycloalkyl" refers to a carbocyclic substituent obtained by removing a hydrogen from a saturated carbocyclic molecule having from 3 to 6 carbon atoms. A "(C_3-C_6)cycloalkyl" may be a monocyclic ring, examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Alternatively, a cycloalkyl may contain more than one ring, such as a (C_4-C_6)bicycloalkyl. The term "(C_4-C_6)bicycloalkyl" refers to a bicyclic system containing 4 to 8 carbon atoms. The bicycloalkyl may be fused, such as bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, bicyclo[2.2.0]hexane, bicyclo[3.1.0]hexane, bicyclo[3.2.0]heptane and bicyclo[3.3.0]octane. The term "bicycloalkyl" also includes bridged bicycloalkyl systems such as, but not limited to, bicyclo[2.2.1]heptane and bicyclo[1.1.1]pentane.
The term "optionally substituted \((C_3-C_6)\)cycloalkyl" refers to a \((C_3-C_6)\)cycloalkyl, as defined above, in which one or more hydrogen atoms are replaced by a substituent selected from the group consisting of halogen, oxo, cyano, hydroxy, \(-SF_5\), nitro, \(-N(R^4)(R^5)\), \(-N(R^4)C(=O)R^5\), \(-N(R^4)C(=O)\)OR\(^5\), \(-C(=O)N(R^4)(R^5)\), \(-O-C(=O)N(R^4)(R^5)\), \(-C(=O)R^4\), \(-C(=O)\)OR\(^4\), and \((C_3-C_6)\)cycloalkyl, in which \(R^4\) and \(R^5\) are each independently hydrogen or optionally substituted \((C_1-C_6)\)alkyl.

The term "\((C_6-C_{10})\)aryl" refers to an aromatic substituent containing from 6 to 10 carbon atoms, consisting of one ring or two fused rings. Examples of such aryl substituents include, but are not limited to, phenyl and naphthyl. The \((C_6-C_{10})\)aryl may also include phenyl and naphthyl substituents that are optionally fused to a \((C_3-C_6)\)cycloalkyl ring (e.g., bicyclo[4.2.0]octa-1,3,5-trienyl) or a \((5-\text{to}\ 6-\text{membered})\)heterocycloalkyl ring (e.g., dihydrobenzofuranyl, benzodioxolyl, and oxisoindolinyl) as defined herein, wherein a group having such a fused aryl group as a substituent is attached to a carbon atom of the aryl. When the aryl is phenyl, it is also referred to herein as an "optionally substituted phenyl".

The term "optionally substituted \((C_6-C_{10})\)aryl" refers to a \((C_6-C_{10})\)aryl, as defined above, in which one or more hydrogen atoms are replaced by a substituent selected from the group consisting of halogen, cyano, hydroxy, \(-SF_5\), nitro, \(-N(R^4)(R^5)\), \(-N(R^4)C(=O)R^5\), \(-N(R^4)C(=O)\)OR\(^5\), \(-O-C(=O)N(R^4)(R^5)\), \(-C(=O)R^4\), \(-C(=O)\)OR\(^4\), and \((C_3-C_6)\)cycloalkyl, in which \(R^4\) and \(R^5\) are each independently hydrogen or optionally substituted \((C_1-C_6)\)alkyl.

The term "heterocycloalkyl," as used herein, refers to a cycloalkyl as defined above, wherein at least one of the ring carbon atoms is replaced with a heteroatom selected from nitrogen, oxygen or sulfur. A "\((4-\text{to}\ 10-\text{membered})\)heterocycloalkyl" refers to a heterocycloalkyl substituent as defined above containing a total of 4 to 10 ring atoms, wherein at least one of the ring atoms is a heteroatom selected from oxygen, nitrogen, or sulfur. A heterocycloalkyl may be a single ring with up to 10 total members. Alternatively, a heterocycloalkyl as defined above may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (i.e., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is attached to the group may be the at least one heteroatom, when the heteroatom is a nitrogen having the appropriate valence, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom when the heteroatom is a nitrogen having the appropriate valence, or it may be bound to a ring carbon atom, where the ring carbon atom may
be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a
different ring from the at least one heteroatom.

Also included in the definition of "heterocycloalkyl" are heterocycloalkyls that are fused to a
(C_{6}-C_{10})aromatic ring or a (5- to 10-membered)heteroaromatic ring. When such a fused
heterocycloalkyl group is substituted with one or more substituents, the one or more substituents,
unless otherwise specified, are each bound to a heteroatom of the heterocycloalkyl group when the
heteroatom is nitrogen having the appropriate valence or to a carbon atom of the heterocycloalkyl
group. Examples of heterocycloalkyl rings include, but are not limited to, azetidinyl, dihydrofuranyl,
dihydrothiophenyl, tetrahydrothiophenyl, tetrahydrofuranyl, tetrahydrothiapizynyl, tetrahydropropyrazolyl,
tetrahydrooxazinyl, tetrahydropropyrimidinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl,
octahydrobenzothiazolyl, imidazolidinyl, pyrrolidinyl, piperidinyl, pyrroolidinyl, oxazolidinyl,
thiazolidinyl, pyrazolidinyl, thiomorpholinyl, tetrahydropropyranyl, tetrahydrothiazinyl,
tetrahydrothiadiazinyl, tetrahydrooxazolyl, morpholinyl, oxetanyl, tetrahydrodiazinyl, oxazinyl,
oxathiazinyl, quinuclidinyl, chromanly, isochromanly, dihydrobenzoxazinyl, indolinyl, isoindolyl,
dihydrobenzofuranyl, tetrahydroquinolyl, isochromyl, dihydro-1H-isoindolyl, 2-
azabicyclo[2.2.1]heptanonyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanonyl and the like.
Further examples of heterocycloalkyl rings include tetrahydrofuran-2-yl, tetrahydrofuran-3-yl,
imidazolin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl,
piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, 1,3-
oxazolidin-3-yl, 1,4-oxazepan-4-yl, isoazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,2-
tetrahydrothiazin-2-yl, 1,3-thiazinan-3-yl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-
oxazin-4-yl, oxazolidinonyl, 2-oxo-piperidinyl (e.g., 2-oxo-piperidin-1-yl), and the like.

The term "optionally substituted heterocycloalkyl" [e.g., optionally substituted (4- to 6-
membered)heterocycloalkyl] refers to a heterocycloalkyl, as defined above, in which one or more
hydrogen atoms, where chemically permissible, are replaced by a substituent selected from the
group consisting of halogen, oxo, cyano, hydroxy, -SF_5, nitro,
-N(R^1)(R^5), -N(R^1)(C(=O)(R^5), -N(R^4)(C(=O)-OR^5, -C(=O)-N(R^4)(R^5), -O-
-C(=O)(R^4)(R^6), -C(=O)-R^4, -C(=O)-OR^4, and (C_3-C_6)cycloalkyl, in which R^4 and R^5 are each
independently hydrogen or optionally substituted (C_1-C_6)alkyl.

The term "(5- to 14-membered)heteroaryl" refers to a heteroaryl ring having from 5 to 14
ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur),
with the remaining ring atoms being independently selected from the group consisting of carbon,
oxogen, nitrogen, and sulfur. A "(5- to 6-membered)heteroaryl" refers to a heteroaryl ring having
from 5 to 6 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A "(6-membered)heteroaryl" refers to a heteroaryl ring having 6 ring atoms. A "(5-membered)heteroaryl" refers to a heteroaryl ring having 5 ring atoms in which at least one of the ring atoms is a heteroatom. A heteroaryl may consist of a single ring or 2 or 3 fused rings. Examples of heteroaryls include, but are not limited to, 6-membered ring substituents such as pyridinyl, pyrazinyl, pyrimidinyl and pyridazinyl; 5-membered heteroaryls such as triazolyl, imidazolyl, furanyl, isoxazolyl, isothiazolyl, 1,2,3- 1,2,4, 1,2,5-, or 1,3,4-oxadiazolyl, oxazolyl, thiophenyl, thiazolyl, and pyrazolyl; 6/5-membered fused ring substituents such as indolyl, indazolyl, benzofurany1, benzimidazolyl, benzothienyl, benzoxadiazolyl, benzothiazolyl, isobenzothiofurany1, benzothiofurany1, benzisoxazolyl, benzoxazolyl, furanopyridinyl, purinyl, imidazopyridinyl, pyrrolopyridinyl, pyrazolo pyridinyl, thienopyridinyl, triazolopyrimidinyl, triazolopyridinyl (e.g., [1,2,4]triazolo[1,5-a]pyridin-2-yl), and anthranilyl; and 6/6-membered fused ring substituents such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, oxochromenyl, and 1,4-benzoxazinyl. In a group that has a heteroaryl substituent, the ring atom of the heteroaryl substituent that is bound to the group may be the at least one heteroatom when the heteroatom is nitrogen having the appropriate valence, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heteroaryl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom when the heteroatom is a nitrogen having the appropriate valence or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom, or where the ring carbon atom may be in a different ring from the at least one heteroatom.

It is to be understood that the "(5- to 14-membered)heteroaryl" may be optionally fused to a (C3-C6)cycloalkyl group, or to a (4- to 10-membered)heterocycloalkyl group, as defined herein. A group having such a fused heteroaryl group as a substituent is attached to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group when the heteroatom is nitrogen having the appropriate valence. Such a fused heteroaryl group may be substituted with up to four substituents; the substituents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group when the heteroatom is nitrogen having the appropriate valence.
The terms "optionally substituted (5- to 14-membered)heteroaryl", "optionally substituted (5- to 6-membered)heteroaryl" and "optionally substituted (5- to 6-membered)nitrogen-containing heteroaryl" refer to a (5- to 14-membered)heteroaryl, a (5- to 6-membered)heteroaryl, and a (5- to 6-membered)nitrogen-containing heteroaryl, as defined above, in which one or more hydrogen atoms are replaced, where chemically permissible, by a substituent selected from the group consisting of halogen, oxo, cyano, hydroxy, -SF₅, nitro, -N(R¹)(R²), -N(R³)(C(=O)R⁴), -N(R⁵)(C(=O)-OR⁶), -C(=O)-N(R⁷)(R⁸), -O-C(=O)N(R⁹)(R¹⁰), -C(=O)-R¹¹, -C(=O)-OR¹², and (C₃₋C₈)cycloalkyl, in which R⁴ and R⁵ are each independently hydrogen or optionally substituted (C₁₋C₈)alkyl. The substituent can be attached to the heteroaryl moiety at any available carbon atom or to a heteroatom when the heteroatom is nitrogen having the appropriate valence.

The term "hydrogen" refers to a hydrogen substituent, and may be depicted as -H.

The term "hydroxy" or "hydroxyl" refers to -OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents are attached include, for example, alcohols, enols and phenol.

The term "cyano" (also referred to as "nitrile") means -CN, which also may be depicted:

\[ \begin{array}{c}
\text{\ce{N=C}} \\
\text{\ce{\equiv}} \\
\text{\ce{\equiv}}
\end{array} \]

The term "oxo" means a =O group.

If a substituent is described as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro substituent, and difluoroalkyl is alkyl substituted with two fluoro substituents. It should be recognized that if there is more than one substitution on a substituent, each non-hydrogen substituent may be identical or different (unless otherwise stated).

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. If a carbon of a substituent is described as being optionally substituted with one or more of a list of substituents, one or more of the hydrogens on the carbon (to the extent there are any) may separately and/or together be replaced with an independently selected optional substituent. If a nitrogen of a substituent is described as being optionally substituted with one or more of a list of substituents, one or more of the hydrogens on the nitrogen (to the extent there are any) may each be replaced with an independently selected optional
substituent. As a further example, when there are optional substituents that can be present, e.g., $R^{10}$ or $R^{11}$, those substituents are as specified in the present specification, and when not present, the atom to which the optional substituent could be attached (i.e., C or N) would have the requisite number of hydrogens attached.

This specification uses the terms “substituent,” “radical,” and “group” interchangeably.

If a substituent is described as being optionally substituted with up to a particular number of non-hydrogen substituents, that substituent may be either (1) not substituted; or (2) substituted by up to that particular number of non-hydrogen substituents or by up to the maximum number of substitutable positions on the substituent, whichever is less. Thus, for example, if a substituent is described as a heteroaryl optionally substituted with up to 3 non-hydrogen substituents, then any heteroaryl with less than 3 substitutable positions would be optionally substituted by up to only as many non-hydrogen substituents as the heteroaryl has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) would be optionally substituted with up to one non-hydrogen substituent. To illustrate further, if an amino nitrogen is described as being optionally substituted with up to 2 non-hydrogen substituents, then the nitrogen will be optionally substituted with up to 2 non-hydrogen substituents if the amino nitrogen is a primary nitrogen, whereas the amino nitrogen will be optionally substituted with up to only 1 non-hydrogen substituent if the amino nitrogen is a secondary nitrogen.

If substituents are described as being “independently selected” from a group, each substituent is selected independent of the other(s). Each substituent therefore may be identical to or different from the other substituent(s).

As used herein, unless specified, the point of attachment of a substituent can be from any suitable position of the substituent.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any of the ring-forming atoms in that ring that are substitutable.

“Subject” may refer to warm-blooded animals such as, for example, pigs, cows, chickens, horses, guinea pigs, mice, rats, gerbils, cats, rabbits, dogs, monkeys, chimpanzees, and humans.

“Pharmacologically acceptable” indicates that the substance or composition must be compatible, chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or a subject.

“Isomer” means “stereoisomer” and “geometric isomer” as defined below.
"Stereoisomer" refers to compounds that possess one or more chiral centers, which may each exist in the R or S configuration. Stereoisomers include all diastereomeric, enantiomeric and epimeric forms as well as racemates and mixtures thereof.

"Geometric isomer" refers to compounds that may exist in cis, trans, anti, entgegen (E), and zusammen (Z) forms as well as mixtures thereof.

As used herein the terms "Formula I", "Formula II", and "Formula III" may be hereinafter referred to as "compound(s) of the invention." Such terms are also defined to include all forms of the compounds of Formulas I through III including hydrates, solvates, isomers, crystalline and non-crystalline forms, isomorphs, polymorphs, and metabolites thereof. For example, the compounds of Formulas I through III, or pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The compounds of the invention may exist as clathrates or other complexes. Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the compounds of the present invention containing two or more organic and/or inorganic components, which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J. Pharm. Sci., 64 (8), 1269-1288 by Halebian (August 1975).

Compounds of the invention may exist as geometric isomers. The compounds of the invention may possess one or more asymmetric centers, thus existing as two, or more, stereoisomeric forms. The present invention includes all the individual stereoisomers and geometric isomers of the compounds of the invention and mixtures thereof. Individual enantiomers can be obtained by resolution, chiral chromatography, or other methods well-known to those skilled in the art, or by using the relevant enantiomeric reactant or reagent in the synthesis.

The carbon-carbon bonds of the compounds of the invention may be depicted herein using a solid line (———), a solid wedge (▁▁▁▁▁▁), or a dotted wedge (· · · · · ·). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g., specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of
either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that the stereoisomer shown is present. When present in racemic compounds, solid and dotted wedges are used to define relative stereochemistry, rather than absolute stereochemistry. Racemic compounds possessing such indicated relative stereochemistry are marked with (+/-). For example, unless stated otherwise, it is intended that the compounds of the invention can exist as stereoisomers, which include cis and trans isomers, optical isomers such as R and S enantiomers, diastereomers, geometric isomers, rotational isomers, conformational isomers, atropisomers, and mixtures thereof. The compounds of the invention may exhibit more than one type of isomerism, and consist of mixtures thereof (such as racemates and diastereomeric pairs). Also included are acid addition or base addition salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

The present invention also includes all pharmaceutically acceptable isotopically labeled compounds, which are identical to those recited in Formulas I through III except that one or more atoms are replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature. Examples of isotopes suitable for inclusion in the compounds of the present invention include, but are not limited to, isotopes of hydrogen, such as $^2$H, $^3$H; carbon, such as $^{11}$C, $^{13}$C, and $^{14}$C; chlorine, such as $^{35}$Cl; fluorine, such as $^{18}$F; iodine, such as $^{123}$I and $^{125}$I; nitrogen, such as $^{13}$N and $^{15}$N; oxygen, such as $^{15}$O, $^{17}$O, and $^{18}$O; phosphorus, such as $^{32}$P; and sulfur, such as $^{35}$S. Certain isotopically labeled compounds of the present invention, for example those incorporating a radioactive isotope, may potentially be useful in drug and/or substrate tissue distribution studies (e.g., assays). The radioactive isotopes tritium, i.e., $^3$H, and carbon-14, i.e., $^{14}$C, may be particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, i.e., $^2$H, may afford certain advantages resulting from potentially greater metabolic stability, for example, potentially increased in vivo half-life or potentially reduced dosage requirements and, hence, may be preferred in some circumstances. Substitution with positron-emitting isotopes, such as $^{11}$C, $^{18}$F, $^{15}$O and $^{13}$N, may be useful in positron emission tomography (PET) studies for examining substrate receptor occupancy. Isotopically
labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Schemes and/or in the Examples and Preparations, by using an appropriate isotopically labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g., D$_2$O, acetone-$d_6$, or DMSO-$d_6$. Compounds of the present invention, as well as the compounds exemplified in Examples 1-22 described below, include isotopically labeled versions of these compounds, such as, but not limited to, the deuterated and tritiated isotopes and all other isotopes discussed above.

The compounds of this invention may be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt may potentially be administered to a subject (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term " pharmaceutically acceptable salt" refers to a salt prepared by combining a compound of the invention with an acid whose anion, or a base whose cation, is generally considered suitable for consumption by a subject. Pharmaceutically acceptable salts may be particularly useful in pharmaceutical compositions because of their potentially greater aqueous solubility relative to the parent compound.

Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible may include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally may include but are not limited to aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids may include but are not limited to acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate,
benzoate, anthranilate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sulfanilate, cyclohexylaminosulfonate, β-hydroxybutyrate, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrote, pivalate, thiocyanate, and undecanoate.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In another embodiment, base salts may be formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine (N-methylglucamine), olamine, tromethamine and zinc salts.

Organic salts may be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethlenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, and procaine. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl (C₁-C₆) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamy sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others.

In one embodiment, hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts.

Also within the scope of the present invention are so-called “prodrugs” of the compound of the invention. Thus, certain derivatives of the compound of the invention that may have little or no pharmacological activity themselves can, if administered into or onto the body, be converted into the compound of the invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as “prodrugs.” Further information on the use of prodrugs may be found in “Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and V. Stella) and “Bioreversible Carriers in Drug Design,” Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association). Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of the
present invention with certain moieties known to those skilled in the art as "pro-moieties" as described, for example, in "Design of Prodrugs" by H. Bundgaard (Elsevier, 1985).

This invention also encompasses compounds of the invention containing protective groups. One skilled in the art will appreciate that compounds of the invention can also be prepared with certain protecting groups that may be useful for purification or storage and can be removed before use. The protection and deprotection of functional groups is described in "Protective Groups in Organic Chemistry", edited by J. F. W. McOmie, Plenum Press (1973) and "Protective Groups in Organic Synthesis", 3rd edition, T. W. Greene and P. G. M. Wuts, Wiley-Interscience (1999).

Compounds

The compounds of Formula I, as depicted above, have a fused bicyclic core represented by 3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione. On the left side of the core, the pyridinone ring is substituted with R^6, R^7, and a (5- to 14-membered)heteroaryl moiety represented by X, wherein X is further substituted with R^1; and on the right side of the core the pyrazinone ring is substituted with R^4b, R^4c, R^5a, R^5b and a pendant cyclopropabenzofuranyl moiety represented by the following structure:

![Diagram of the molecule structure]

In certain embodiments, in Formula I as depicted above, R^1, R^2a, R^2b, R^3a, R^4b, R^5a, R^5b, R^6, R^7, R^10, R^11, and y are as defined above; and X is represented by:

Xi) a (5- to 6-membered)heteroaryl containing 1-3 heteroatoms;

Xii) a (5-membered)heteroaryl containing 1-3 heteroatoms; or

Xiii) a (6-membered)heteroaryl containing 1-3 heteroatoms.

In certain other embodiments, the (5- to 6-membered)heteroaryl is selected from the group consisting of triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, isothiazolyl, thiazolyl, isoxazolyl, oxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl.

In certain embodiments, the (6-membered)heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl.
In certain other embodiments, the (5-membered)heteroaryl is selected from the group consisting of triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, isothiazolyl, thiazolyl, isoxazolyl, and oxazolyl.

In certain other embodiments, X is a (5-membered)heteroaryl, wherein the heteroaryl is imidazolyl.

In certain other embodiments, X is a (5-membered)heteroaryl, wherein the heteroaryl is triazolyl.

In certain other embodiments, in Formula I as depicted above, X is represented by one of the embodiments as immediately described above, wherein:

R¹, where chemically permissible, is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₃-C₆)cycloalkyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)(R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴;

R₂⁸ and R₂⁹, where chemically permissible, at each occurrence, are independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)(R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or R₂⁸ and R₂⁹ together with the carbon atom(s) to which they are attached form a (C₃-C₆)cycloalkyl or a (4- to 10-membered)heterocycloalkyl, wherein the (C₃-C₆)cycloalkyl and the (4- to 10-membered)heterocycloalkyl are optionally substituted with one to three R⁸;

R₃⁸ and R₃⁹, where chemically permissible, are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)(R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or R₃⁸ and R₃⁹ together with the carbon atom to which they are attached form a (C₃-C₆)cycloalkyl, wherein the (C₃-C₆)cycloalkyl is optionally substituted with one to three R⁸;
R^5a and R^5b, at each occurrence, are independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF_5, nitro, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl, optionally substituted (C_2-C_6)alkynyl, optionally substituted thio(C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_1-C_6)alkoxy(C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted phenyl, -N(R^4)(R^5), -N(R^4)(C=(O)R^5), -C(=O)N(R^4)(R^5), -O-C(=O)N(R^4)(R^5), -C(=O)-R^4, and -C(=O)-OR^4; or R^5a and R^5b together with the carbon atom to which they are attached form a (C_3-C_8)cycloalkyl, wherein said (C_3-C_8)cycloalkyl is optionally substituted with one to three R^8;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, cyano, -SF_5, nitro, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl, optionally substituted (C_2-C_6)alkynyl, optionally substituted thio(C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_1-C_6)alkoxy(C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted phenyl, -N(R^4)(R^5), -N(R^4)(C=(O)R^5), -C(=O)N(R^4)(R^5), -O-C(=O)N(R^4)(R^5), -C(=O)-R^4, -C(=O)-OR^4, and -OR^6; provided that R^6 and R^7 cannot both be hydroxy;

R^8, at each occurrence, is independently selected from the group consisting of cyano, halogen, hydroxy, -SF_5, nitro, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and optionally substituted (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R^9 is selected from the group consisting of hydrogen and optionally substituted (C_1-C_6)alkyl;

y is an integer selected from 1, 2, 3 or 4;

ring B is optionally substituted with one to three R^{10}, wherein each R^{10} is independently selected from the group consisting of halogen, cyano, hydroxy, -SF_5, nitro, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl, optionally substituted (C_2-C_6)alkynyl, optionally substituted thio(C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_3-C_8)cycloalkyl, -N(R^4)(R^5), -N(R^4)(C=(O)R^5), -C(=O)N(R^4)(R^5), -O-C(=O)N(R^4)(R^5), -C(=O)-R^4, -C(=O)-OR^4; or two R^{10} substituents taken together with the carbon atom(s) to which they are attached form an optionally substituted (C_3-C_8)cycloalkyl;

ring D is optionally substituted with one to four R^{11}, wherein each R^{11} is independently selected from the group consisting of halogen, cyano, hydroxy, -SF_5, nitro, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl, optionally substituted (C_2-C_6)alkynyl, optionally substituted thio(C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted (4- to 6-
membered)heterocycloalkyl; \(-N(R^4)(R^5), \quad -N(R^4)(C=O)R^5, \quad -C(=O)N(R^4)(R^5), \quad -O-C(=O)N(R^4)(R^5), \quad -C(=O)-R^4, \quad -C(=O)-OR^4; \) and
\[ R^4 \text{ and } R^5, \text{ at each occurrence, are each independently selected from hydrogen or optionally substituted } (C_1-C_6)\text{alkyl}; \]
provided that the compound is not 7-(4-methyl-1H-imidazol-1-yl)-2-[[5-(trifluoromethyl)-1,1a-
dihydro-6bH-cycloprop[a][1]benzofuran-6b-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione.

In certain other embodiments, in Formula I as depicted above, \( X \) is a (5-
membered)heteroaryl selected from the group consisting of triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, isothiazolyl, thiazolyl, isoxazolyl, and oxazolyl, wherein:
\[ R^1 \text{ is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, optionally substituted } (C_1-C_6)\text{alkyl, and optionally substituted } (C_1-C_6)\text{alkoxy; wherein the } (C_1-C_6)\text{alkyl and } (C_1-
C_6)\text{alkoxy are optionally substituted with one to three substituents selected from halogen, oxo,}
\]
cyano, hydroxy, or \(-\text{SF}_5; \)
\[ R^{2a} \text{ and } R^{2b} \text{ are each independently selected from hydrogen, halogen, cyano, hydroxy or optionally substituted } (C_1-C_6)\text{alkyl}; \]
\[ R^{4a}, \quad R^{4b}, \quad R^{5a} \text{ and } R^{5b} \text{ are each independently selected from the group consisting of}
\]
hydrogen, halogen, cyano, hydroxy, \( \text{oxo, -SF}_5; \) optionally substituted \((C_1-C_6)\text{alkyl, and optionally substituted (C}_1-C_6)\text{alkoxy, wherein the (C}_1-C_6)\text{alkyl and (C}_1-
C_6)\text{alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or } -\text{SF}_5; \)
\[ R^5 \text{ and } R^7 \text{ are each independently selected from the group consisting of hydrogen, cyano, halogen, }-\text{SF}_5, \text{ optionally substituted } (C_1-C_6)\text{alkyl, and optionally substituted } (C_1-C_6)\text{alkoxy, wherein the}
\]
\( (C_1-C_6)\text{alkyl and } (C_1-C_6)\text{alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or } -\text{SF}_5; \)
y is 1;
\[ \text{ring } B \text{ is optionally substituted with one to two } R^{10}, \text{ wherein each } R^{10} \text{ is independently selected from}
\]
halogen, cyano, hydroxy, \( -\text{SF}_5, \text{ optionally substituted } (C_1-C_6)\text{alkyl, and optionally substituted (C}_1-
C_6)\text{alkoxy, wherein the (C}_1-C_6)\text{alkyl and (C}_1-C_6)\text{alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or } -\text{SF}_5; \) and
\[ \text{ring } D \text{ is optionally substituted with one to three } R^{11}, \text{ wherein each } R^{11} \text{ is independently selected from the group consisting of halogen, cyano, hydroxy, optionally substituted } (C_1-C_6)\text{alkyl, optionally substituted (C}_1-C_6)\text{alkoxy, } -\text{SF}_5, \quad -\text{N(R}^4)(R^5), \text{ nitro, and optionally substituted (C}_5-
C_6)\text{cycloalkyl, wherein the (C}_1-C_6)\text{alkyl, (C}_1-C_6)\text{alkoxy, and (C}_3-C_6)\text{cycloalkyl are optionally }
\]
substituted with one to three substituents independently selected from halogen, cyano, hydroxy, \(-\text{SF}_5\), and optionally substituted \((\text{C}_1-\text{C}_6)\)alkyl, wherein \(R^4\) and \(R^5\) are each independently selected from hydrogen or optionally substituted \((\text{C}_1-\text{C}_6)\)alkyl;

provided that the compound is not 7-(4-methyl-1H-imidazol-1-yl)-2-[[5-(trifluoromethyl)-1,1a-
di-hydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione.

In certain embodiments, in Formula I as immediately described above:

\(R^1\) is an optionally substituted \((\text{C}_1-\text{C}_6)\)alkyl, wherein the \((\text{C}_1-\text{C}_6)\)alkyl is substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or \(-\text{SF}_5\); and

\(R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a}\) and \(R^{5b}\) are each independently

i) hydrogen; or

ii) optionally substituted \((\text{C}_1-\text{C}_6)\)alkyl, wherein the \((\text{C}_1-\text{C}_6)\)alkyl is substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or \(-\text{SF}_5\).

In certain other embodiments, \(R^1\) is methyl; and \(R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a}\) and \(R^{5b}\) are each independently hydrogen.

In certain other embodiments, \(R^1\) is methyl; \(R^{2a}, R^{2b}, R^{5a}\) and \(R^{5b}\) are each independently hydrogen; and one of \(R^{4a}\) and \(R^{4b}\) is hydrogen and the other is methyl.

In another embodiment, \(R^1\) is methyl; one of \(R^{2a}\) and \(R^{2b}\) is hydrogen and the other is methyl; and \(R^{4a}, R^{4b}, R^{5a}\) and \(R^{5b}\) are each independently hydrogen.

To further elucidate the compounds of the present invention, wherein X is a (5-
membered)heteroaryl ring and the (5-membered)heteroaryl ring is imidazolyl or triazolyl, the following subgenuses are described below:

Formula II, as depicted below, is a subset of Formula I, as depicted above, wherein X is a (5-membered)heteroaryl wherein the heteroaryl is imidazolyl, \(R^1\) is a \((\text{C}_1-\text{C}_6)\)alkyl wherein the \((\text{C}_1-
\text{C}_6)\)alkyl is methyl, \(R^6\) and \(R^7\) are each hydrogen, \(y\) is 1, and the cyclopropabenzofuranyl moiety is attached via the benzylic position of the cyclopropabenzofuranyl moiety:
In certain embodiments, in Formula II, as depicted above, or a pharmaceutically acceptable salt thereof:

R^1 is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, optionally substituted (C_1-C_6)alkyl, and optionally substituted (C_1-C_6)alkoxy; wherein the (C_1-C_6)alkyl and (C_1-C_6)alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF_5;

R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a} and R^{5b} are each independently selected from hydrogen, halogen, cyano, hydroxy or optionally substituted (C_1-C_6)alkyl;

ring B is optionally substituted with one to two R^{10}, wherein each R^{10} is independently selected from halogen or optionally substituted (C_1-C_6)alkyl; and

ring D is optionally substituted with one to three R^{11}, wherein each R^{11} is independently selected from halogen, optionally substituted (C_1-C_6)alkyl, and optionally substituted (C_1-C_6)alkoxy; provided that the compound is not 7-(4-methyl-1H-imidazol-1-yl)-2-[[5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione.

In certain embodiments, Formula II is as immediately described above:

R^1 is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, (C_1-C_6)alkyl, and (C_1-C_6)alkoxy; wherein the (C_1-C_6)alkyl and (C_1-C_6)alkoxy are optionally substituted with one to three fluoro atoms;

R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a} and R^{5b} are each independently selected from hydrogen or (C_1-C_6)alkyl, wherein the (C_1-C_6)alkyl is methyl;

ring B is optionally substituted with one to two R^{10}, wherein each R^{10} is selected from:

i) halogen selected from fluoro or chloro, or
ii) (C<sub>1</sub>-C<sub>6</sub>)alkyl, wherein the (C<sub>1</sub>-C<sub>6</sub>)alkyl is methyl; and ring D is optionally substituted with one to three R<sup>11</sup>, wherein each R<sup>11</sup> is selected from:

i) halogen selected from fluoro or chloro;

ii) optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, wherein the (C<sub>1</sub>-C<sub>6</sub>)alkyl is methyl and the methyl is optionally substituted with one to three fluoro (e.g., fluoromethyl, difluoromethyl, or trifluoromethyl); and

iii) optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkoxy, wherein the (C<sub>1</sub>-C<sub>6</sub>)alkoxy is methoxy and the methoxy is optionally substituted with one to three fluoro (e.g., fluoromethoxy, difluoromethoxy, or trifluoromethoxy).

In any of the above-mentioned embodiments for Formula II, R<sup>1</sup> is a (C<sub>1</sub>-C<sub>6</sub>)alkyl wherein the alkyl is methyl. In certain embodiments, when R<sup>1</sup> is methyl, the R<sup>1</sup>-X moiety of Formula I is 4-methyl-1H-imidazol-1-yl.

Formula III, as depicted below, is a subset of Formula I as depicted above, wherein X is a (5-membered)heteroaryl, wherein the heteroaryl is triazolyl, R<sup>1</sup> is a (C<sub>1</sub>-C<sub>6</sub>)alkyl, wherein the (C<sub>1</sub>-C<sub>6</sub>)alkyl is methyl, R<sup>6</sup> and R<sup>7</sup> are each hydrogen, y is 1, and the cyclopropabenzofurananyl moiety is attached via the benzylic position of the cyclopropabenzofurananyl moiety:

![Formula III](image)

In certain embodiments, in Formula III, as depicted above, or a pharmaceutically acceptable salt thereof:

R<sup>1</sup> is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, and optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkoxy; wherein the (C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>1</sub>-C<sub>6</sub>)alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF<sub>5</sub>;
R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a} and R^{5b} are each independently selected from hydrogen, halogen, cyano, hydroxy or optionally substituted (C_1-C_6)alkyl;

ring B is optionally substituted with one to two R^{10}, wherein each R^{10} is independently selected from halogen or optionally substituted (C_1-C_6)alkyl; and

ring D is optionally substituted with one to three R^{11}, wherein each R^{11} is independently selected from halogen, optionally substituted (C_1-C_6)alkyl, and optionally substituted (C_1-C_6)alkoxy;

In certain embodiments, Formula III is as immediately described above:

R^1 is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, (C_1-C_6)alkyl, and (C_1-C_6)alkoxy; wherein the (C_1-C_6)alkyl and (C_1-C_6)alkoxy are optionally substituted with one to three fluoro atoms;

R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a} and R^{5b} are each independently selected from hydrogen or (C_1-C_6)alkyl, wherein the (C_1-C_6)alkyl is methyl;

ring B is optionally substituted with one to two R^{10}, wherein each R^{10} is selected from:

i) halogen selected from fluoro or chloro, or

ii) (C_1-C_6)alkyl, wherein the (C_1-C_6)alkyl is methyl; and

ring D is optionally substituted with one to three R^{11}, wherein each R^{11} is selected from:

i) halogen selected from fluoro or chloro;

ii) optionally substituted (C_1-C_6)alkyl, wherein the (C_1-C_6)alkyl is methyl and the methyl is optionally substituted with one to three fluoro (e.g., fluoromethyl, difluoromethyl, or trifluoromethyl); and

iii) optionally substituted (C_1-C_6)alkoxy, wherein the (C_1-C_6)alkoxy is methoxy and the methoxy is optionally substituted with one to three fluoro (e.g., fluoromethoxy, difluoromethoxy, or trifluoromethoxy).

In any of the above-mentioned embodiments for Formula III, R^1 is a (C_1-C_6)alkyl wherein the alkyl is methyl. In certain embodiments, when R^1 is methyl, the R^1-X moiety is 3-methyl-1H-1,2,4-triazol-1-yl.

In certain other embodiments, compounds of the present invention are selected from the group consisting of:

7-(4-methyl-1H-imidazol-1-yl)-2-[[1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-(4-methyl-1H-imidazol-1-yl)-2-((1aS,6bS)-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
7-(4-methyl-1H-imidazol-1-yl)-2-\{[(1aR,6bR)-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aS,6bS)-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aR,6bR)-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aR,6bR)-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aR,6bR)-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aS,6bS)-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aR,6bR)-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aR,6bR)-4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aR,6bR)-4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-\{[(1aS,6bS)-5-(difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-\{[(1aR,6bR)-5-(difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-\{[(1aS,6bS)-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-[4-(hydroxymethyl)-1H-imidazol-1-yl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-(4-methyl-1H-imidazol-1-yl)-2-\{[(1aS,6bS)-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-(4-methyl-1H-imidazol-1-yl)-2-\{[(1aR,6bR)-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-\{[(1aS,6bS)-4-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-\{[(1aR,6bR)-4-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-\{[(1aS,6bS)-3-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-\{[(1aR,6bR)-3-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-\{[(1aS,6bS)-3-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione; and

2-\{[(1aR,6bR)-3-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione; or

the pharmaceutically acceptable salts thereof.
In certain embodiments, the present invention is directed to a pharmaceutical composition comprising selected compounds of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Pharmacology

Alzheimer's disease (AD) research indicates that the disease is associated with the buildup of plaques in variable shapes and sizes in the brain. The primary plaques associated with AD are composed of amyloid beta peptides (Aβ). Aβ is produced when the amyloid precursor protein (APP) undergoes successive proteolysis by the aspartyl proteases β- and γ-secretase (Haas et al., "Trafficking and proteolytic processing of APP." Cold Spring Harbor Perspect. Med., 2011). γ-Secretase is a large complex consisting of at least four different integral proteins, one of which is presenilin and has been identified as the catalytic component that harbors the catalytic aspartates (De Strooper, Bart et al., “Presenilins and γ-Secretase: Structure, Function, and Role in Alzheimer's Disease.” Cold Spring Harbor Perspect. Med. 2012;2:a006304). Presenilin 1 and 2 were first discovered as sites of missense mutations responsible for early-onset Alzheimer's disease. The encoded multipass membrane proteins were subsequently found to be the catalytic components of γ-secretases, membrane-embedded aspartyl protease complexes responsible for generating the carboxyl terminus of the amyloid beta protein from the amyloid protein precursor. (De Strooper, Bart et al.; 2012). Accordingly, targeting the γ-secretase complex for drug discovery has become a main focus of Alzheimer's disease research.

The compounds of the present invention are believed to be γ-secretase modulators, which modulate the γ-secretase complex such that longer pathogenic Aβ peptides (i.e., Aβ42) are reduced and shorter Aβ species (i.e., Aβ37 and/or Aβ38) are increased.

Formulations

In another embodiment, the present invention comprises pharmaceutical compositions. Such pharmaceutical compositions comprise a compound of the invention presented with a pharmaceutically acceptable carrier. The carrier can be a solid, a liquid, or both, and may be formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compounds. A compound of the invention may be coupled with suitable polymers as targetable drug carriers. Other pharmacologically active substances may also be present.

Pharmaceutical compositions may be adapted for potential delivery orally, rectally, parenterally, or topically.
Oral solid dose forms may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention. In another embodiment, the oral dose form may be in a powder or granule form. In another embodiment, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of the invention may be combined with one or more adjuvants. Such capsules or tablets may contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, the oral dose form may be a liquid dose form. Oral liquid dosage forms may include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (i.e., water). Such compositions also may comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In another embodiment, the present invention comprises a parenteral dose form, which may include, for example, forms suitable for potential delivery by subcutaneous injection, intravenous injection, intraperitoneal injection, intramuscular injection, intrasternal injection, and infusion. Injectable preparations (i.e., sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing, wetting, and/or suspending agents.

In another embodiment, the present invention comprises a topical dose form, which may include transdermal dose forms, such as transdermal patches or iontophoresis devices, intraocular dose forms, or intranasal or inhalable dose forms. Topical dose forms may also include, for example, topical gels, sprays, ointments, and creams. A topical formulation may include a compound which enhances absorption or penetration of an active ingredient through the skin or other affected areas. A transdermal patch may include either the reservoir and porous membrane type or a solid matrix variety. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, Finnin and Morgan, J. Pharm. Sci., 88 (10), 955-958 (1999).

Ophthalmic topical formulations may include, for example, eye drops wherein the active is dissolved or suspended in a suitable carrier. A typical ocular or aural formulation may be in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other
ocular or aural formulations may include ointments, biodegradable (e.g., absorbable gel sponges, collagen) and non-biodegradable (e.g., silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as cross-linked polyacrylic acid, polyvinyl alcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gellan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be potentially delivered by iontophoresis.

For intranasal or inhalable dose forms, active compounds may be conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant. Intranasal formulations may be in the form of a dry powder (either alone; as a mixture, for example, in a dry blend with lactose; or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) for delivery from a dry powder inhaler or as an aerosol spray for delivery from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropylene. For potential intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the present invention comprises a rectal dose form. Such rectal dose form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other carrier materials and dose forms known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

The compounds of the present invention, or their pharmaceutically acceptable salts, may be prepared by the methods described below, together with synthetic methods known in the art of organic chemistry, or modifications and derivatizations that are familiar to those of ordinary skill in
the art. The starting materials used herein are commercially available or may be prepared by routine methods known in the art [such as those methods disclosed in standard reference books such as the Compendium of Organic Synthetic Methods, Vol. I-XII (published by Wiley-Interscience)]. Preferred methods include, but are not limited to, those described below.

During any of the following synthetic sequences, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991; and T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, which are hereby incorporated by reference.

Compounds of the present invention, or their pharmaceutically acceptable salts, can be prepared according to the reaction Schemes discussed herein below. Unless otherwise indicated, the substituents in the Schemes are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill. It will be understood by one skilled in the art that the various symbols, superscripts and subscripts used in the schemes, methods and examples are used for convenience of representation and/or to reflect the order in which they are introduced in the schemes, and are not intended to necessarily correspond to the symbols, superscripts or subscripts in the appended claims. The schemes are representative of methods useful in synthesizing the compounds of the present invention. They are not to constrain the scope of the invention in any way.

Schemes

When intermediates used to synthesize compounds of the present invention incorporate a basic center, their suitable acid addition salts may be employed in synthetic pathways. Such suitable addition salts include but are not limited to those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, hydroiodic, boric, fluoroboric, phosphoric, nitric, carbonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, ethanesulfonic, fumaric, lactic, maleic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, and trifluoroacetic acids. Suitable organic acids generally include but are not limited to aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include but are not limited to acetate, trifluoroacetate, formate, propionate, succinate, lactate, maleate, fumarate, benzoate,
p-hydroxybenzoate, phenylacetate, mandelate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, adipate, butyrate, camphorate, cyclopentanepropionate, dodecylsulfate, heptanoate, hexanoate, nicotinate, 2-naphthalenesulfonate, oxalate, 3-phenylpropionate, pivalate, and undecanoate.

Furthermore, where intermediates used to prepare compounds of the invention carry an acidic moiety, suitable salts thereof may be employed for synthesis. Such salts include alkali metal salts, e.g., lithium, sodium, or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands such as amines or quaternary ammonium cations. Organic salts of such acid intermediates may be made from primary, secondary or tertiary amines such as methyamine, diethylamine, ethyleneediamine or trimethyamine. Quaternary amines may be prepared by reaction of tertiary amines with agents such as lower alkyl (C₁-C₆) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others.

Scheme 1

Scheme 1 above illustrates one synthetic sequence for the preparation of compounds depicted by Formula I. In the initial step of the synthesis, as depicted, an appropriate ester of a compound of Formula 1.1, wherein R¹ is typically a (C₁-C₆)alkyl such as methyl, ethyl, tert-butyl and the like, is heated in the presence of an aqueous acid such as hydrochloric acid to furnish the
corresponding pyridinone acid of Formula 1.2. During this initial step, the $R^1$-$X$, $R^6$ and $R^7$ substituents of Formula 1.1 should be represented by the same moieties as are desired in the final product, or a protected variation thereof. For example, the final product of Example 1 can be prepared utilizing reaction Scheme 1, where $R^1$ is represented by methyl, $X$ is represented by imidazolyl, and $R^6$ and $R^7$ of Formula 1.1 are each represented by hydrogen.

Next, the acid intermediate of Formula 1.2 is subjected to an amide coupling and in situ cyclization reaction with an amino alcohol of Formula 1.3 using an appropriate amide coupling reagent such as HATU [O-(7-azabenzotriazol-1-yl)-$N,N',N'$-tetramethyluronium hexafluorophosphate]. The reaction is carried out in the presence of a suitable base such as $N,N$-diisopropylethylamine, and in a solvent such as dichloromethane or $N,N$-dimethylformamide. During this step, $y$ of Formula 1.3 should be represented by an integer as desired in the final product, and the A, $R^{2a}$, $R^{2b}$, $R^{4a}$, $R^{4b}$, $R^{5a}$, $R^{5b}$ substituents should be represented by the same moieties as are desired in the final product, or a protected variation thereof. For example, the final product of Example 1 can be prepared utilizing reaction Scheme 1, where $R^{2a}$, $R^{2b}$, $R^{4a}$, $R^{4b}$, $R^{5a}$, and $R^{5b}$ are each hydrogen, $y$ is 1, and A represents 5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl.

Scheme 2 illustrates another synthetic sequence for the preparation of compounds of Formula I. Reaction of a chloroaldehyde of Formula 2.1 and an amine of Formula 2.2 using one of many reductive amination protocols known to those skilled in the art provides the chloroalkylamine
of Formula 2.3. For example, this reaction may be carried out by using a reducing agent such as sodium triacetoxyborohydride in a suitable solvent such as methanol. During this step, \( y \) of the amine of Formula 2.2 should be represented by an integer as desired in the final product. The \( R^{5a} \) and \( R^{5b} \) substituents of Formula 2.1 and the \( A, R^{2a}, \) and \( R^{2b} \) substituents of the amine of Formula 2.2 should also be represented by the same moieties as are desired in the final product, or a protected variation thereof.

Following purification, the resultant chloroalkylamine of Formula 2.3 may be isolated and stored as its hydrochloride salt. The final compound of Formula 1 may then be prepared by treating a mixture of the chloroalkylamine of Formula 2.3, the acid of Formula 1.2 (Scheme 1), and a base such as \( N,N \)-diisopropylethylamine with a suitable amide coupling reagent such as BOP-Cl [bis(2-oxo-3-oxazolidinyl)phosphonic chloride], T3P [2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide] or HATU (preferably HATU) in a solvent such as dichloromethane. During this step the \( R^1-X, R^8 \) and \( R^7 \) substituents of Formula 1.2 should be represented by the same moieties as are desired in the final product, or a protected variation thereof.

![Scheme 3](image-url)

**Scheme 3**

Scheme 3 represents several synthetic sequences for the preparation of the aminoalcohol of Formula 1.3, which can readily be envisioned and developed by one skilled in the art. For example, the aminoalcohol of Formula 1.3 may be prepared by carrying out a reductive amination of a ketone of Formula 3.1 with an amine of Formula 2.2 using one of many procedures well known to those skilled in the art.
Another method involves reductive amination of an aldehyde of Formula 3.2 with an amine of Formula 2.2, followed by removal of the tert-butyl(dimethyl)silyl (TBS) protecting group by using a suitable procedure including treatment with methanolic hydrogen chloride or tetrabutylammonium fluoride.

Yet another method involves alkylation of an amine of Formula 2.2 with a bromoalcohol of Formula 3.5. Methods of synthesis for various amines of Formula 2.2, as well as alternative methods of preparation of aminoalcohols of Formula 1.3, are exemplified in the Experimental Section.

A person skilled in the art, utilizing these disclosures in combination with what is commonly known in the art, may further generalize those syntheses to allow access to a wide variety of amines of Formula 2.2 and aminoalcohols of Formula 1.3, including but not limited to variations in which y is represented by an integer as desired in the final product, and A, R²b, R⁴b, R⁴a, and R⁵b substituents are represented by the same moieties as are desired in the final product, or a protected variation thereof.

Scheme 4 illustrates one synthetic sequence for the preparation of compounds of Formula 1.1 where R¹-X = 4-methylimidazol-1-yl or 3-methyltriazol-1-yl. A 3-aminopyridine compound of Formula 4.1 is brominated using N-bromosuccinimide (NBS) in a solvent such as a mixture of DMSO and water. During this initial step the R⁶ and R⁷ substituents are represented by the same moieties as are desired in the final product, or a protected variation thereof. The resulting
intermediate of Formula 4.2 is then heated with sodium methoxide in a suitable solvent such as 1,4-dioxane to afford the methoxy compound of Formula 4.3. The intermediate of Formula 4.3 is then treated with a mixture of acetic anhydride and formic acid to afford a formamide of Formula 4.4, which is alkylated with chloroacetone in the presence of potassium iodide and a base such as cesium carbonate in a suitable solvent such as N,N-dimethylformamide. The resulting intermediate of Formula 4.5 is then heated in the presence of NH₄OAc in acetic acid to furnish the imidazole derivative of Formula 4.6. Finally, the compound of Formula 1.1 can be prepared by subjecting the intermediate of Formula 4.6 to a carbonylation/esterification reaction. This transformation may be carried out by heating a solution of the bromo compound of Formula 4.6 and a base such as triethylamine in an appropriate alcohol solvent ("ROH"), wherein R is typically a (C₁-C₆)alkyl such as methyl or ethyl, under an atmosphere of CO in the presence of a suitable palladium catalyst such as Pd(dppf)Cl₂·dichloromethane [(1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), dichloromethane complex) to provide the ester of Formula 1.1.
Scheme 5

A) Suzuki coupling: R^1-X-B(OH)_2, "Pd", base

B) CH-activation: "Pd", 5-membered heteroaryl such as
provide compounds of Formula 1.1 wherein R^1-X- is

C) Chan-Lam coupling: Cu_2O or Cu(OAc)_2, 5-membered heteroaryl such as
provide compounds of Formula 1.1 wherein R^1-X- is

D) Suzuki coupling: R^1-X-Br, "Pd", base

where X = a 5- to 6-membered heteroaryl ring

Scheme 5 depicts alternative synthetic sequences for the preparation of compounds of Formula 1.1. In a first step, a pyridyl derivative of Formula 5.1 is oxidized with an oxidizing agent such as mCPBA [3-chloroperoxybenzoic acid] in a suitable solvent such as dichloroethane to afford the corresponding N-oxide of Formula 5.2. During this initial step the R^5 and R^7 substituents of Formula 5.1 are represented by the same moieties as are desired in the final product, or a
protected variation thereof. The N-oxide of Formula 5.2 is then heated in the presence of TMSCN [trimethylsilyl cyanide] and a base such as triethylamine in a solvent such as acetonitrile to afford the nitrile intermediate of Formula 5.3. The corresponding ester may then be prepared from Formula 5.3 in two steps by subjecting Formula 5.3 to sodium methoxide in a solvent such as THF, followed by treatment with an appropriate alcohol solvent ("ROH"), wherein R is typically a (C₁-C₆)alkyl such as methyl, ethyl and the like, and an acid such as hydrochloric acid. The ester of Formula 5.5 is a versatile intermediate that allows introduction of a variety of heterocycles R¹-X. For example, Formula 5.5 may be subjected to a Suzuki coupling with a heteroarylboron acid, using methods well known to those skilled in the art [see *Tetrahedron* 2002, 58, 9633-9695]. Alternatively, the compound of Formula 5.5 may be coupled to a heterocycle X using a direct arylation approach [see D. Lapointe et al., *J. Org. Chem.* 2011, 76, 749-759, and references therein]. For example, the compound of Formula 5.5 may be coupled to 2-methyl-1,3-oxazole [Formula 5.7 where R¹ = Me] by heating in the presence of a suitable palladium catalyst such as allylpalladium chloride dimer and a base such as potassium carbonate in a solvent such as 1,4-dioxane, to afford the intermediate of Formula 1.1 where R¹-X = 2-methyl-1,3-oxazol-5-yl.

Alternatively, the compound of Formula 5.5 may be converted to the corresponding boronate of Formula 5.6, using a palladium-catalyzed cross coupling with a diboron reagent such as 5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane in the presence of potassium acetate and a palladium catalyst such as Pd(dppf)Cl₂-dichloromethane in a solvent such as 1,4-dioxane. The resulting boronate intermediate of Formula 5.6 can in turn be subjected to a Suzuki coupling with a heteroaryl halide to afford the final compound of Formula 1.1. Another method for the introduction of a heterocycle X involves the use of a Chan-Lam coupling [see *Tetrahedron Lett.* 2003, 44, 3863-3865, and *Synthesis* 2008, 5, 795-799]. For example, the boronate of Formula 5.6 may be coupled to a substituted imidazole of Formula 5.8 or to a substituted triazole of Formula 5.9, by heating with a suitable copper source such as copper(I) oxide or copper(II) acetate in a solvent such as methanol in the presence of air to afford the intermediate of Formula 1.1 where X = imidazol-1-yl or triazol-1-yl.
Scheme 6

A) Suzuki coupling: R\(^1\)X-B(OH)\(_2\), "Pd", base

B) CH-activation: "Pd", 5-membered heteroaryls such as
provide compounds of Formula I wherein R\(^1\)-X- is

C) Chan-Lam coupling: Cu\(_2\)O or Cu(OAc)\(_2\), 5-membered heteroaryls such as
provide compounds of Formula I wherein R\(^1\)-X- is

D) Suzuki coupling: R\(^1\)X-Br, "Pd", base
where X = a 5- to 6-membered heteroaryl ring

E) "Pd", and a heteroaryl such as
provide compounds of Formula I wherein R\(^1\)-X- is

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Scheme 6 illustrates yet another set of synthetic sequences for the preparation of compounds of Formula I. Heating an intermediate of Formula 6.1 in an acid such as hydrochloric acid affords the pyridinone acid intermediate of Formula 6.2. During this initial step, the \( R^6 \) and \( R^7 \) substituents of Formula 6.1 are represented by the same moieties as are desired in the final product, or a protected variation thereof. Next, the acid of Formula 6.2 may be subjected to a coupling/cyclization reaction with an aminoalcohol of Formula 1.3 (Scheme 1) to afford an intermediate of Formula 6.3 using chemistry described in Scheme 1. During this step, \( y \) of Formula 1.3 should be represented by an integer as desired in the final product, and the \( R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{10} \) and \( R^{11} \) substituents should be represented by the same moieties as are desired in the final product, or a protected variation thereof.

An alternative synthesis of the intermediate of Formula 6.3 involves heating a mixture of the intermediate of Formula 6.2, dibromoethane, and a base such as cesium carbonate in a solvent such as \( N,N \)-dimethylformamide to afford a lactone of Formula 6.4. During this initial step, the \( R^6 \) and \( R^7 \) substituents of Formula 6.1 are represented by the same moieties as are desired in the final product, or a protected variation thereof. The resultant intermediate of Formula 6.3 may then be subjected to an amidation reaction with an amine of Formula 2.2 (Scheme 2). This transformation may be carried using a number of different conditions. For example, the lactone of Formula 6.2 and the amine of Formula 2.2 may be heated in the presence of a base such as 1,3,4,6,7,8-hexahydro-2H-pyrindido[1,2-a]pyrimidine (TBD) in a solvent such as \( N,N \)-dimethylformamide, followed by addition of ethyl trifluoroacetate to afford the lactam of Formula 6.3 wherein \( R^{4a} = R^{5b} = R^{5a} = R^{5b} = R^{10} = R^{11} \). During the amidation step, \( y \) of Formula 2.2 should be represented by an integer as desired in the final product.

The final compound, Formula I, may then be formed directly from Formula 6.3 or via the boronate of Formula 6.5, using the strategies discussed in Scheme 5. Alternatively, compounds of Formula I where heterocycle X is linked to the pyridinone ring via a C–N bond may be formed by palladium-catalyzed cross coupling. For example, the triazole of Formula 6.6 may be coupled to Formula 6.3 by heating in the presence of a palladium catalyst such as tris(dibenzylideneacetone)dipalladium(0) and a suitable ligand such as di-tert-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane and base such as potassium phosphate in a solvent such as toluene to afford the final compound of Formula I where \( X = 1,2,4 \)-triazol-1-yl.
Scheme 7 illustrates another synthetic sequence for the preparation of compounds of Formula I, where \( R^{4a} = R^{4b} = R^{5a} = R^{5b} = H \). The method involves heating a mixture of a compound of Formula 1.2 (Scheme 1), dibromoethane, and a base such as cesium carbonate in a solvent such as \( N,N \)-dimethylformamide to afford the lactone intermediate of Formula 7.1. During this initial step, the \( R^1 \), \( X \), \( R^6 \) and \( R^7 \) substituents of Formula 1.2 are represented by the same moieties as are desired in the final product, or a protected variation thereof. The lactone of Formula 7.1 may then be reacted with an amine of Formula 2.2 (from Scheme 2) in the presence of a reagent such as DIBAL (diisobutylaluminum hydride) or bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct in a solvent such as THF to afford the amide alcohol of Formula 7.2. During this step, \( y \) of Formula 2.2 should be represented by an integer as desired in the final product, and the \( R^{2a} \), \( R^{2b} \), \( R^{10} \) and \( R^{11} \) substituents should be represented by the same moieties as are desired in the final product, or a protected variation thereof. The intermediate of Formula 7.2 may be reacted with methanesulfonyl chloride in the presence of a base such as triethylamine in a solvent such as THF, followed by treatment with a base such as 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine (TBD) to afford the compound of Formula I wherein \( R^{4a} = R^{4b} = R^{5a} = R^{5b} = H \). Alternatively, the ring closure may be carried out in a stepwise fashion by first converting the alcohol of Formula 7.2 into the corresponding chloride by treatment with thionyl chloride, followed by deprotonation of the amide NH with a suitable base such as lithium bis(trimethylsilyl)amide to afford the final compound of
Formula I. Alternatively, a solution of lactam 7.1 and amine 2.2 in N,N-dimethylformamide may be treated with 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine (TBD) in N,N-dimethylformamide to form intermediate 7.2, which is then directly converted to Formula I in the same pot via addition of ethyl trifluoroacetate.

Compounds of Formula I where X is imidazolyl and R¹ is hydroxymethyl may be prepared in one step from the corresponding compound of Formula I where X is imidazolyl and R¹ is methyl. This transformation can be carried out via incubation with microsomes from a suitable species such as monkey in the presence of magnesium chloride and nicotinamide adenine dinucleotide phosphate (NADPH) in a suitable buffer such as potassium phosphate (pH 7.4).
A number of routes can be envisioned to access intermediates of Formula 2.2, where $R^{2a} = R^{2b} = \text{H}$, $R^{10} = \text{methyl}$, $y = 1$, $R^{10}$ is connected to the quaternary carbon atom adjacent to the benzofuran oxygen atom, and the aminomethyl substituent is connected to the benzylic position. One approach commences with bromination or iodination of a phenol of Formula 9.1 using a suitable halogenating reagent such as $N$-bromosuccinimide (NBS) or $N$-iodosuccinimide (NIS). During this step, the $R^{11}$ substituent should be represented by the same moiety as is desired in the final product, or a protected variation thereof. The resultant phenol intermediate of Formula 9.2 is then reacted with benzyl chloromethyl ether in the presence of a suitable base such as potassium carbonate and in a solvent such as acetonitrile to afford an intermediate of Formula 9.3. This compound is then subjected to a Sonogashira coupling with trimethyl(prop-2-yn-1-yl)silane using a copper source such as copper(II) iodide and a palladium catalyst such as...
dichlorobis(triphenylphosphine)palladium(II) in triethylamine. The trimethylsilyl protecting group is subsequently removed using a fluoride source such as tetra-N-butylammonium fluoride (TBAF) in a solvent such as tetrahydrofuran to afford an intermediate of Formula 9.5. This compound can then be heated in the presence of a platinum catalyst such as di-μ-chloro-dichlorobis(ethylene)diplatinum(III) in a solvent such as toluene to afford benzo furan intermediate 9.6. The benzyl protecting group is then removed via hydrogenolysis using palladium hydroxide on carbon in cyclohexene. Cyclopropanation of the benzo furan 2,3-double bond can be carried under a number of conditions such as the Simmons-Smith reaction. For example, the intermediate of Formula 9.7 is treated with diethylzinc and diiodomethane in a suitable solvent such as dichloromethane to afford the cyclopropyl benzo furan alcohol intermediate of Formula 9.8. The primary alcohol in the intermediate of Formula 9.8 may then be converted to the corresponding primary amine using a number of procedures well known to those skilled in the art. For example, this functional group interconversion can be accomplished via a Mitsunobu reaction with phthalimide followed by deprotection using a reagent such as hydrazine monohydrate in a solvent such as dichloromethane and methanol to afford the desired amine of Formula 2.2.

Scheme 10

\[ \text{Reducting agent} \]

where \( R^{2a} = R^{2b} = H \), and \( y = 1 \)
Scheme 10 displays an alternative synthetic route to intermediates of Formula 2.2 where R^{2a} = R^{2b} = H, y = 1, R^{10} is connected to the quaternary carbon atom adjacent to the benzofuran oxygen atom, and the aminomethyl substituent is connected to the benzylic position. In this approach, the phenol of Formula 9.2 undergoes a 1,4-addition to an alkyne derivative of Formula 10.1 in the presence of a base such as potassium carbonate in a solvent such as acetonitrile. During this step, the R^{10} and R^{11} substituents should be represented by the same moiety as is desired in the final product, or a protected variation thereof. The resulting compound of Formula 10.2 is then subjected to an intramolecular Heck reaction using a suitable palladium catalyst such as bis(tri-tert-butylphosphine)palladium(0) in the presence of a base such as triethylamine in a solvent such as acetonitrile. The resultant benzofuran intermediate of Formula 10.3 is then subjected to cyclopropanation using trimethylsulfoxonium iodide in dimethyl sulfoxide in the presence of a base such as potassium tert-butoxide. The ester is immediately hydrolyzed to the corresponding acid of Formula 10.4 using a suitable base such as potassium hydroxide or potassium tert-butoxide. The final step in the sequence involves conversion of the carboxylic acid of Formula 10.4 to the amine of Formula 2.2. This functional group interconversion can be carried out under a number of different conditions known to those skilled in the art. For example, amide coupling of acid 10.4 with ammonium hydroxide and a coupling reagent such as 1,1'-carbonyldiimidazole delivers the primary amide of Formula 10.5, which is subsequently reduced using a suitable reducing agent such as bis(2-methoxyethoxy)aluminum hydride in a solvent such as toluene.

**Experimental Procedures and Working Examples**

The following illustrate the synthesis of various compounds of the present invention. Additional compounds within the scope of this invention may be prepared using the methods illustrated in these Examples, either alone or in combination with techniques generally known in the art.

Experiments were generally carried out under inert atmosphere (nitrogen or argon), particularly in cases where oxygen- or moisture-sensitive reagents or intermediates were employed. Commercial solvents and reagents were generally used without further purification. Anhydrous solvents were employed where appropriate, generally AcroSeal® products from Acros Organics or DriSolv® products from EMD Chemicals. In other cases, commercial solvents were passed through columns packed with 4Å molecular sieves, until the following QC standards for water were attained: a) <100 ppm for dichloromethane, toluene, N,N-dimethylformamide and...
tetrahydrofuran; b) <180 ppm for methanol, ethanol, 1,4-dioxane and diisopropylamine. For very sensitive reactions, solvents were further treated with metallic sodium, calcium hydride or molecular sieves, and distilled just prior to use. Products were generally dried under vacuum before being carried on to further reactions or submitted for biological testing. Mass spectrometry data is reported from either liquid chromatography-mass spectrometry (LCMS), atmospheric pressure chemical ionization (APCI) or gas chromatography-mass spectrometry (GCMS) instrumentation. Chemical shifts for nuclear magnetic resonance (NMR) data are expressed in parts per million (ppm, δ) referenced to residual peaks from the deuterated solvents employed. In some examples, chiral separations were carried out to separate enantiomers of certain compounds of the invention (in some examples, the separated enantiomers are designated as ENT-1 and ENT-2, according to their order of elution). In some examples, the optical rotation of an enantiomer was measured using a polarimeter. According to its observed rotation data (or its specific rotation data), an enantiomer with a clockwise rotation was designated as the (+)-enantiomer and an enantiomer with a counterclockwise rotation was designated as the (-)-enantiomer. Racemic compounds are indicated by the presence of (+/-) adjacent to the structure; in these cases, indicated stereochemistry represents the relative (rather than absolute) configuration of the compound’s substituents.

Reactions proceeding through detectable intermediates were generally followed by LCMS, and allowed to proceed to full conversion prior to addition of subsequent reagents. For syntheses referencing procedures in other Examples or Methods, reaction conditions (reaction time and temperature) may vary. In general, reactions were followed by thin-layer chromatography or mass spectrometry, and subjected to work-up when appropriate. Purifications may vary between experiments: in general, solvents and the solvent ratios used for eluents/gradient were chosen to provide appropriate Rs or retention times.

Example 1

7-(4-Methyl-1H-imidazol-1-yl)-2-[[5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (1)

(The compound of Example 1 was previously disclosed in U.S. Provisional Patent Application No. 61/973,436, filed on April 1, 2014 as Example 19. While this compound is not encompassed by the claims of the present application, it is being exemplified herein to provide additional synthetic methodology).
Step 1. Synthesis of 4-[(2-iodo-4-(trifluoromethyl)phenoxy)methyl]-2,2-dimethyl-1,3-dioxolane (C1).

Diisopropyl azodicarboxylate (8.2 mL, 42 mmol) was added slowly, in a drop-wise manner, to a 0 °C solution of (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (5.5 g, 42 mmol) and triphenylphosphine (10.9 g, 42 mmol) in tetrahydrofuran (80 mL). 2-Iodo-4-(trifluoromethyl)phenol (8.0 g, 28 mmol) was slowly added to the 0 °C reaction mixture, which was then allowed to stir at room temperature for 6 hours. After removal of solvent in vacuo, the residue was partitioned between water and ethyl acetate, and the organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Silica gel chromatography (Eluent: 10% ethyl acetate in hexane) afforded the product as a light yellow liquid. Yield: 6.5 g, 16 mmol, 57%. ¹H NMR (400 MHz, CDCl₃) δ 8.02 (br s, 1H), 7.58 (br d, J=8.6 Hz, 1H), 6.88 (d, J=8.6 Hz, 1H), 4.48-4.56 (m, 1H), 4.23 (dd, J=8.4, 6.2 Hz, 1H), 4.18 (dd, half of ABX pattern, J=9.5, 4.2 Hz, 1H), 4.04-4.11 (m, 2H), 1.49 (s, 3H), 1.42 (s, 3H).

Step 2. Synthesis of 3-[2-iodo-4-(trifluoromethyl)phenoxy]propane-1,2-diol (C2).

A solution of C1 (6.5 g, 16 mmol) in acetic acid (3.2 mL, 56 mmol) and water (0.29 mL, 16 mmol) was stirred at room temperature for 18 hours, whereupon it was concentrated under reduced pressure. The residue was washed with pentane, and the resulting solid was taken into the
following step without further purification. Yield: 5.25 g, 14.5 mmol, 91%. GCMS m/z 362 [M+]. 1H NMR (400 MHz, CDCl₃) δ 8.01-8.04 (m, 1H), 7.60 (br d, J=8.6 Hz, 1H), 6.89 (d, J=8.6 Hz, 1H), 4.13-4.23 (m, 3H), 3.83-3.97 (m, 2H), 2.71 (d, J=4.5 Hz, 1H), 2.05 (dd, J=6.2, 6.0 Hz, 1H).


To a solution of C2 (5.25 g, 14.5 mmol) in N,N-dimethylformamide (50 mL) was added imidazole (1.1 g, 16 mmol), followed by slow addition of tert-butyl(dimethyl)silyl chloride (2.4 g, 16 mmol). After 6 hours at room temperature, the reaction mixture was diluted with ice water and then extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo; silica gel chromatography (Eluent: 5% ethyl acetate in hexanes) provided the product as a light yellow liquid. Yield: 4.12 g, 8.65 mmol, 60%. NMR (400 MHz, CDCl₃) δ 8.01-8.03 (m, 1H), 7.58 (br d, J=8.6 Hz, 1H), 6.88 (d, J=8.6 Hz, 1H), 4.05-4.17 (m, 3H), 3.84-3.92 (m, 2H), 2.58 (d, J=5.8 Hz, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).


Dess-Martin periodinane [1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one; 11.0 g, 25.9 mmol] was added to a 0 °C solution of C3 (4.12 g, 8.65 mmol) in dichloromethane (40 mL), and the reaction mixture was stirred for 14 hours. Excess oxidant was removed via filtration through a pad of diatomaceous earth; the filtrate was diluted with water and extracted with dichloromethane. The combined organic layers were concentrated in vacuo, and the crude product was used in the following step without additional purification. Yield: 3.7 g, 7.8 mmol, 90%. 1H NMR (400 MHz, CDCl₃) δ 8.05-8.07 (m, 1H), 7.57 (br d, J=8.6 Hz, 1H), 6.70 (d, J=8.6 Hz, 1H), 4.94 (s, 2H), 4.59 (s, 2H), 0.96 (s, 9H), 0.15 (s, 6H).

Step 5. Synthesis of 3-((tert-butyl(dimethyl)silyloxy)methyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-3-ol (C5).

Methyllithium (1.6 M solution in diethyl ether, 9.2 mL, 15 mmol) was slowly added to a -78 °C solution of C4 (3.5 g, 7.4 mmol) in tetrahydrofuran (30 mL), and the reaction mixture was stirred at this temperature for 5 hours. Aqueous ammonium chloride solution was then slowly added, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to provide the crude product (2.1 g), which was
used directly in the next step. $^1$H NMR (400 MHz, CDCl$_3$), product peaks only: δ 7.62-7.65 (m, 1H), 7.51-7.55 (m, 1H), 6.91 (d, J=8.6 Hz, 1H), 4.49 (s, 2H), 3.84 (AB quartet, $J_{AB}$=9.8 Hz, $\Delta v_{AB}$=11.3 Hz, 2H), 0.94 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).

An aqueous solution of p-toluenesulfonic acid (10%, 11 mL) was slowly added to a solution of C5 (from the previous step; 2.1 g, 6.0 mmol) in acetone (20 mL), and the reaction mixture was allowed to stir at room temperature for 14 hours. Acetone was removed via concentration in vacuo, and the aqueous residue was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure; silica gel chromatography (Eluent: 5% ethyl acetate in hexane) afforded the product (435 mg) as a light yellow liquid. Also isolated was the tert-butyl(dimethyl)silyl-protected derivative of C6; this was subjected to p-toluenesulfonic acid in a similar manner, providing an additional 150 mg of the product. Total yield: 585 mg, 2.71 mmol, 37% over two steps. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.00 (br s, 1H), 7.73 (br s, 1H), 7.56-7.63 (m, 2H), 4.90 (br d, $J$=5.3 Hz, 2H), 1.68 (t, $J$=5.6 Hz, 1H).

Step 7. Synthesis of [5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methanol (C7).
To a 0 °C solution of C6 (100 mg, 0.46 mmol) in dichloromethane (10 mL) was added diiodomethane (744 mg, 2.78 mmol), followed by slow addition of diethylzinc (1 M solution in hexanes, 1.39 mL, 1.39 mmol) at the same temperature. The reaction mixture was allowed to slowly warm to room temperature, whereupon it was stirred for 3 hours. It was then quenched via addition of saturated sodium thiosulfate solution, and extracted with dichloromethane; the combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 30% ethyl acetate in hexanes) provided the product as a yellow oil. Yield: 50 mg, 0.22 mmol, 48%. GCMS m/z 230 [M$^+$]. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.75-7.78 (m, 1H), 7.47 (br d, $J$=8.3 Hz, 1H), 7.00 (d, $J$=8.8 Hz, 1H), 4.98 (dd, $J$=5.9, 5.4 Hz, 1H), 4.93 (dd, $J$=5.5, 1.8 Hz, 1H), 3.93 (dd, half of ABX pattern, $J$=11.8, 5.9 Hz, 1H), 3.73 (dd, half of ABX pattern, $J$=11.9, 5.3 Hz, 1H), 1.26 (dd, $J$=6.2, 5.8 Hz, 1H), 0.40 (dd, $J$=6.5, 1.8 Hz, 1H).

Step 8. Synthesis of [5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl methanesulfonate (C8).
Triethylamine (0.27 mL, 1.9 mmol) and methanesulfonyl chloride (61 µL, 0.79 mmol) were added to a 0 °C solution of C7 (150 mg, 0.65 mmol) in dichloromethane (10 mL), and the reaction mixture was allowed to slowly warm to room temperature. After it had stirred for 6 hours, the reaction mixture was quenched via addition of saturated aqueous sodium bicarbonate solution, and extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo to afford the product (120 mg). This material was used directly in the following step.

**Step 9. Synthesis of 1-[(5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methanamine (C9).**

To a 0 °C solution of C8 (from the previous step; 120 mg, ≤0.39 mmol) in methanol (1 mL) was added methanolic ammonia (5 mL) and the reaction mixture was heated at 70 °C for 16 hours in a sealed tube. It was then evaporated to dryness; the residue was mixed with water and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (Eluent: 10% methanol in dichloromethane) afforded the product as a light yellow gum. Yield: 50 mg, 0.22 mmol, 34% over two steps.

**Step 10. Synthesis of 1-[(2-hydroxyethyl)-5-(4-methyl-1H-imidazol-1-yl)-6-oxo-N-[[5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-1,6-dihydropyridine-2-carboxamide (C11).**

To a solution of C9 (115 mg, 0.502 mmol) in tetrahydrofuran (1 L) was added bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (270 mg, 1.05 mmol). The reaction mixture was heated to 40 °C for 45 minutes, whereupon it was treated with 7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydropyrido[2,1-c][1,4]oxazine-1,6-dione (C10, which may be prepared via the method of C. W. amEnde et al., PCT Int. Appl., WO 2012131539, October 4, 2012) (120 mg, 0.49 mmol) and heated to 65 °C for 5 hours. The reaction was quenched via addition of 1 M aqueous sodium hydroxide solution, and the resulting slurry was diluted with water and extracted with 5% methanol in dichloromethane; the combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Trituration with 10% ethyl acetate in hexanes afforded the product as an off-white solid (100 mg), which was used in the next step without additional purification. LCMS m/z 475.0 [M+H]^+.
Step 11. Synthesis of 1-(2-chloroethyl)-5-(4-methyl-1H-imidazol-1-yl)-6-oxo-N-[(5-
(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6-b-yl)methyl]-1,6-dihydropyridine-2-
carboxamide (C12).

To a -10 °C solution of C11 (from the previous step; 100 mg, ≤21 mmol) in
dichloromethane (10 mL) was added triethylamine (90 μL, 0.65 mmol), followed by drop-wise
addition of methanesulfonyl chloride (70 mg, 0.61 mmol). The reaction mixture was then allowed to
warm to room temperature and stir for 2 hours, whereupon it was diluted with dichloromethane,
was washed with aqueous sodium bicarbonate solution and with saturated aqueous sodium chloride
solution, dried over sodium sulfate, filtered, and evaporated in vacuo. The product was obtained as
a sticky brown solid (100 mg), which was used in the next step without additional purification.

Step 12. Synthesis of 7-(4-methyl-1H-imidazol-1-yl)-2-[(5-(trifluoromethyl)-1,1a-dihydro-6bH-
cylopropa[b][1]benzofuran-6-b-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (1).

To a solution of C12 (from the previous step; 100 mg, ≤20 mmol) in tetrahydrofuran (10
mL) was added 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine (99 mg, 0.71 mmol) and the
reaction mixture was allowed to stir at room temperature for 16 hours. Ice water was added, and
the mixture was evaporated to dryness under reduced pressure; the residue was diluted with water
and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo.

Reversed phase HPLC (Column: YMC-Actus Triart C18, 5 μm; Mobile phase A: 20 mM ammonium bicarbonate in water; Mobile phase B: acetonitrile; Gradient: 10% to 55% B) afforded the product as
an off-white solid. Yield: 18 mg, 39 μmol, 8% over three steps. LCMS m/z 457.0 [M+H]+. 1H NMR
(400 MHz, CDCl3) δ 8.20 (s, 1H), 7.62-7.65 (m, 1H), 7.43 (d, J=7.6 Hz, 1H), 7.40-7.45 (m, 1H),
7.24-7.3 (m, 1H, assumed; partially obscured by solvent peak), 7.09-7.13 (m, 1H), 6.91 (d, J=8.6
Hz, 1H), 4.90-4.94 (m, 1H), 4.86 (d, J=14.7 Hz, 1H), 4.26-4.35 (m, 1H), 4.11-4.20 (m, 1H), 3.54-
3.64 (m, 2H), 3.43 (d, J=14.8 Hz, 1H), 2.28 (s, 3H), 1.25 (dd, J=6.7, 5.8 Hz, 1H), 0.62 (dd, J=7, 2
Hz, 1H).
Examples 2 and 3

7-(4-Methyl-1H-imidazol-1-yl)-2-[(1aS,6bS)-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (2) and 7-(4-Methyl-1H-imidazol-1-yl)-2-[(1aR,6bR)-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (3)
Step 1. Synthesis of 2-iodo-4-(trifluoromethoxy)phenol (C13).

4-(Trifluoromethoxy)phenol (4.0 mL, 31 mmol) was added to a suspension of N-iodosuccinimide (95%, 6.95 g, 29.3 mmol) in acetic acid (2.0 mL, 35 mmol), and the mixture was stirred for 5 minutes. Sulfuric acid (98%, 0.5 mL, 9 mmol) was introduced, and stirring was continued at room temperature for 48 hours, whereupon the reaction mixture was poured into water (100 mL) and extracted with diethyl ether. The combined organic layers were washed with water, washed twice with 1 M aqueous sodium thiosulfate solution, treated with decolorizing carbon, and dried over magnesium sulfate. After the mixture had been filtered through a pad of diatomaceous earth and silica gel, the filtrate was concentrated in vacuo to provide the product as an oil (13.2 g). By \(^1\)H NMR analysis, this product contained a significant quantity of ethyl acetate. Yield, corrected for ethyl acetate: 8.5 g, 28 mmol, 96%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.54 (br d, J=2.6 Hz, 1H), 7.15 (br dd, J=8.9, 2.6 Hz, 1H), 6.99 (d, J=8.9 Hz, 1H).

Step 2. Synthesis of 1-[(benzxyloxy)methoxy]-2-iodo-4-(trifluoromethoxy)benzene (C14).

A solution of C13 (9.30 g, 30.6 mmol) in acetonitrile (100 mL) was treated with potassium carbonate (8.46 g, 61.2 mmol), followed by benzyl chloromethyl ether (6.38 mL, 45.9 mmol). The reaction mixture was allowed to stir at room temperature overnight, whereupon it was partitioned between water and diethyl ether. The combined organic layers were washed with water, dried over
magnesium sulfate, filtered, and concentrated *in vacuo*; purification via silica gel chromatography (Gradient: 0% to 5% ethyl acetate in heptane) provided the product as an oil. Yield: 10.8 g, 25.5 mmol, 83%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.67 (br d, J=2.2 Hz, 1H), 7.30-7.40 (m, 5H), 7.19 (br dd, half of ABX pattern, J=9, 2 Hz, 1H), 7.14 (d, half of AB quartet, J=9.0 Hz, 1H), 5.35 (s, 2H), 4.76 (s, 2H).

**Step 3. Synthesis of (3-[(benzyloxy)methoxy]-5-(trifluoromethoxy)phenyl)prop-2-yn-1-yl)(trimethyl)silane (C15).**

A mixture of C14 (2.80 g, 6.60 mmol), copper(I) iodide (254 mg, 1.33 mmol), and dichlorobis(triphenyolphosphine)palladium(II) (99%, 468 mg, 0.660 mmol) in triethylamine (20 mL) was stirred for 5 minutes, whereupon trimethyl(prop-2-yn-1-yl)silane (80%, 1.85 mL, 9.9 mmol) was added and the reaction mixture was heated to 50 °C. After 5 hours, it was cooled to room temperature and partitioned between diethyl ether and saturated aqueous ammonium chloride solution. The organic layer was washed with 1 M aqueous hydrochloric acid, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The product was obtained as a thick oil, which was used without additional purification. Yield: 2.69 g, 6.58 mmol, quantitative. GCMS m/z 408.2 [M$^+$].

**Step 4. Synthesis of 1-[(benzyloxy)methoxy]-2-(prop-1-yn-1-yl)-4-(trifluoromethoxy)benzene (C16).**

Tetrabutylammonium fluoride (1 M solution in tetrahydrofuran; 10 mL, 10 mmol) was added to a solution of C15 (2.60 g, 6.36 mmol) in tetrahydrofuran (25 mL), and the reaction mixture was stirred at room temperature. After 2 hours, it was partitioned between water and diethyl ether; the organic layer was washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Silica gel chromatography (Gradient: 0% to 5% ethyl acetate in heptane) afforded the product as an oil. Yield: 1.99 g, 5.92 mmol, 93%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29-7.40 (m, 5H), 7.24-7.27 (m, 1H, assumed; partially obscured by solvent peak), 7.17 (d, half of AB quartet, J=9.0 Hz, 1H), 7.08 (br d, half of AB quartet, J=9 Hz, 1H), 5.36 (s, 2H), 4.78 (s, 2H), 2.12 (s, 3H).

**Step 5. Synthesis of 3-[(benzyloxy)methyl]-2-methyl-5-(trifluoromethoxy)-1-benzofuran (C17).**

Compound C16 (1.99 g, 5.92 mmol) and di-mu-chloro-dichlorobis(ethylene)diplatinum(II) (Zeise's dimer; 190 mg, 0.32 mmol) were combined in toluene (20 mL) and heated to 35 °C for 3
hours. After the reaction mixture had cooled to room temperature, silica gel chromatography (Gradient: 0% to 5% ethyl acetate in heptane) provided the product as a solid. Yield: 1.50 g, 4.46 mmol, 75%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29-7.42 (m, 7H), 7.09 (br d, J=8.8 Hz, 1H), 4.61 (s, 2H), 4.57 (s, 2H), 2.44 (s, 3H).


A solution of C17 (1.80 g, 5.35 mmol) in ethanol (25 mL) was treated with palladium hydroxide on carbon (20%, 1.0 g). Cyclohexene (6 mL, 60 mmol) was added, and the reaction mixture was heated at reflux for 5 hours, whereupon it was cooled and treated with additional palladium hydroxide on carbon (1.0 g) and cyclohexene (6 mL, 60 mmol). After being heated overnight at reflux, the reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 50% ethyl acetate in heptane) afforded the product as a white solid. Yield: 787 mg, 3.20 mmol, 60%. GCMS m/z 246.1 [M$^+$]. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.47 (br s, 1H), 7.38 (d, J=8.8 Hz, 1H), 7.10 (br d, J=8.8 Hz, 1H), 4.77 (s, 2H), 2.48 (s, 3H).

Step 7. Synthesis of [1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methanol (C19).

Diethylzinc (1.0 M solution in hexane; 10.4 mL, 10.4 mmol) was cooled in an ice bath, diluted with dichloromethane (10 mL), and treated with a solution of diiodomethane (1.67 mL, 20.7 mmol) in dichloromethane (2 mL). After 5 minutes, a solution of C18 (510 mg, 2.07 mmol) in dichloromethane (10 mL) was added, and stirring was continued for 5 minutes at 0 °C. The reaction mixture was then allowed to warm to room temperature and stir for 4 hours, whereupon it was quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether, and the combined organic layers were dried over magnesium sulfate, filtered, concentrated in vacuo, and purified via silica gel chromatography (Gradient: 5% to 30% ethyl acetate in heptane). The product was obtained as a solid. Yield: 500 mg, 1.9 mmol, 92%. GCMS m/z 260.1 [M$^+$]. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26-7.30 (m, 1H, assumed; largely obscured by solvent peak), 6.98 (br d, J=8.8 Hz, 1H), 6.79 (d, J=8.7 Hz, 1H), 4.14 (d, J=12.1 Hz, 1H), 3.87 (d, J=12.0 Hz, 1H), 1.76 (s, 3H), 1.07 (d, J=6.2 Hz, 1H), 0.62 (d, J=6.2 Hz, 1H).

Step 8. Synthesis of 2-[[1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-1H-isothioindole-1,3(2H)-dione (C20).
1H-Isoindole-1,3(2H)-dione (1.64 g, 11.1 mmol) and triphenylphosphine (2.89 g, 11.0 mmol) were added to a solution of C19 (2.40 g, 9.22 mmol) in tetrahydrofuran (50 mL). Diisopropyl azodicarboxylate (95%, 2.07 mL, 10.2 mmol) was added drop-wise, and the reaction mixture was allowed to stir at room temperature for 2 hours. It was then partitioned between diethyl ether and saturated aqueous sodium chloride solution, and the organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 5% to 50% ethyl acetate in heptane) afforded the product as a thick oil. Yield: 1.6 g, 4.1 mmol, 44%. LCMS m/z 389.8 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.86-7.90 (m, 2H), 7.73-7.77 (m, 2H), 7.61-7.65 (m, 1H), 6.94 (br d, J=8.7 Hz, 1H), 6.75 (d, J=8.7 Hz, 1H), 4.24 (d, J=15.2 Hz, 1H), 3.98 (d, J=15.3 Hz, 1H), 1.92 (s, 3H), 1.12 (d, J=6.3 Hz, 1H), 0.52 (d, J=6.3 Hz, 1H).

**Step 9. Synthesis of 1-[1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6-b-yl]methanamine (C21).**

Hydrazine monohydrate (2.0 mL, 41 mmol) was added to a solution of C20 (1.6 g, 4.1 mmol) in dichloromethane (10 mL) and methanol (10 mL). The reaction mixture was stirred overnight at room temperature, whereupon it was partitioned between 1 M aqueous sodium hydroxide solution and diethyl ether. The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure, providing the product as a thick oil. Yield: 1.0 g, 3.9 mmol, 95%. ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.24 (m, 1H), 6.97 (br d, J=8.7 Hz, 1H), 6.78 (d, J=8.7 Hz, 1H), 3.39 (d, J=14.2 Hz, 1H), 2.86 (d, J=14.0 Hz, 1H), 1.75 (s, 3H), 0.95 (d, J=6.2 Hz, 1H), 0.55 (d, J=6.2 Hz, 1H).

**Step 10. Synthesis of 7-(4-methyl-1H-imidazol-1-yl)-2-[[1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6-b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (C22)**

1,3,4,6,7,8-Hexahydro-2H-pyrimido[1,2-a]pyrimidine (97%, 830 mg, 5.78 mmol) was added to a solution of C21 (1.00 g, 3.86 mmol) and C10 (1.26 g, 5.14 mmol) in N,N-dimethylformamide (4 mL). After 3 hours at room temperature, the reaction mixture was treated with ethyl trifluoroacetate (1.1 mL, 9.2 mmol) and allowed to stir overnight. Aqueous sodium hydroxide solution (1 M, 6 mL, 6 mmol) was added, and the mixture was stirred for 15 minutes at room temperature. The solid was collected via filtration, rinsed with water and with diethyl ether, and azeotroped 3 times with toluene, affording the product as an off-white solid. Yield: 1.68 g, 3.45 mmol, 89%. LCMS m/z 487.4 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃), characteristic peaks: δ 8.21 (s, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.11-7.14
(m, 1H), 6.98 (br d, J=9 Hz, 1H), 6.81 (d, J=8.7 Hz, 1H), 5.05 (d, J=15.2 Hz, 1H), 4.23 (ddd, half of ABXY pattern, J=14, 8, 4 Hz, 1H), 4.15 (ddd, half of ABXY pattern, J=14, 7, 4 Hz, 1H), 3.56 (ddd, half of ABXY pattern, J=13, 7, 4 Hz, 1H), 3.46 (ddd, half of ABXY pattern, J=13, 8, 4 Hz, 1H), 3.18 (d, J=15.2 Hz, 1H), 2.29 (s, 3H), 1.84 (s, 3H), 1.00 (d, J=6.5 Hz, 1H), 0.68 (d, J=6.4 Hz, 1H).

Step 11. Isolation of 7-(4-methyl-1H-imidazol-1-yl)-2-[[1aS,6bS]-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (2) and 7-(4-methyl-1H-imidazol-1-yl)-2-[[1aR,6bR]-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (3).

Compound C22 (1.68 g, 3.45 mmol) was separated into its component enantiomers via supercritical fluid chromatography (Column: Chiral Technologies Chiralpak AD-H, 5 μm; Mobile phase: 30% [0.2% ammonium hydroxide in methanol] in carbon dioxide). Each enantiomer was then dissolved in ethyl acetate (10 mL), passed through a syringe filter, and concentrated in vacuo.

The first-eluting enantiomer was triturated with diethyl ether to afford 3 as a solid. The second-eluting enantiomer was recrystallized from ethyl acetate / heptane to provide 2 as a solid.

3: Yield: 435 mg, 0.894 mmol, 26%. LCMS m/z 487.4 [M+H]+. 1H NMR (400 MHz, CD3OD) δ 8.28 (br s, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.28-7.32 (m, 2H), 7.28 (d, J=7.8 Hz, 1H), 6.96-7.01 (m, 1H), 6.83 (d, J=8.7 Hz, 1H), 4.93 (d, J=15.1 Hz, 1H), 4.13-4.25 (m, 2H), 3.72 (ddd, J=13, 6, 5 Hz, 1H), 3.50 (ddd, J=13, 8, 5 Hz, 1H), 3.39 (d, J=15.2 Hz, 1H), 2.23 (d, J=0.9 Hz, 3H), 1.85 (s, 3H), 1.14 (d, J=6.4 Hz, 1H), 0.57 (d, J=6.5 Hz, 1H).

2: Yield: 447 mg, 0.919 mmol, 27%. LCMS m/z 487.4 [M+H]+. 1H NMR (400 MHz, CD3OD) δ 8.28 (br s, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.28-7.32 (m, 2H), 7.28 (d, J=7.8 Hz, 1H), 6.96-7.01 (m, 1H), 6.83 (d, J=8.8 Hz, 1H), 4.93 (d, J=15.1 Hz, 1H), 4.13-4.25 (m, 2H), 3.72 (ddd, J=13, 6, 5 Hz, 1H), 3.50 (ddd, J=13, 8, 5 Hz, 1H), 3.39 (d, J=15.2 Hz, 1H), 2.23 (d, J=0.8 Hz, 3H), 1.85 (s, 3H), 1.14 (d, J=6.4 Hz, 1H), 0.57 (d, J=6.4 Hz, 1H). Compound 2 was subjected to X-ray structural analysis (see below), which established its absolute stereochemistry. Compound 2 was more potent than its enantiomer 3 (see Table 7); this potency difference was observed for all of the separated enantiomers in these Examples, and was used to assign the absolute stereochemistry in all cases, in direct analogy with 2 and 3.
Single Crystal X-Ray Analysis of Compound 2

Data collection was performed on a Bruker APEX diffractometer at room temperature. Data collection consisted of omega and phi scans.

The structure was solved by direct methods using SHELX software suite in the space group P1. The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters.

The conformations of the two molecules in the asymmetric unit are slightly different from one other. Both molecules have the same stereochemistry.

All hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms.

Analysis of the absolute structure using likelihood methods (Hooft 2008) was performed using PLATON (Spek 2010). The results indicate that the absolute structure has been correctly assigned. The method calculates that the probability that the structure is correct is 100.0%. The Hooft parameter is reported as 0.07 with an esd of 0.06.

The final R-index was 5%. A final difference Fourier revealed no missing or misplaced electron density.

Pertinent crystal, data collection, and refinement information is summarized in Table 1. Atomic coordinates, bond lengths, bond angles, and displacement parameters are listed in Tables 2 – 5.

Software and References


Table 1. Crystal data and structure refinement for 2.

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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 2. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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Symmetry transformations used to generate equivalent atoms.

Table 4. Anisotropic displacement parameters (Å² x 10^3) for 2. The anisotropic displacement factor exponent takes the form: \(-2\pi^2[h^2a^2U^{11} + \ldots + 2ha^*b^*U^{12}]\).

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Table 5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\AA^2 \times 10^3$) for 2.
Examples 4 and 5

2-[[1aS,6bS)-3-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-
a]pyrazine-1,6-dione (4) and 2-[[1aR,6bR)-3-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-
6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-
pyrido[1,2-a]pyrazine-1,6-dione (5)

Tripropan-2-yl borate (43.6 g, 232 mmol) was added to a solution of 4-bromo-3-fluorophenyl trifluoromethyl ether (50.0 g, 193 mmol) in toluene (400 mL) and tetrahydrofuran (100 mL), and the mixture was cooled to −78 °C. n-Butyllithium (2.5 M solution; 92.7 mL, 232 mmol) was then added drop-wise, at a rate that maintained the reaction temperature below −60 °C, and the reaction mixture was stirred at −70 °C for 4 hours. After the reaction mixture had been warmed to −20 °C, it was quenched via addition of aqueous hydrochloric acid (2 M, 200 mL), and then stirred at room temperature (20 °C) for 40 minutes. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to afford the product (43 g) as a white solid, which was carried directly to the next step.


To a 20 °C solution of C23 (from the previous step; 43 g, ≤193 mmol) in dichloromethane (300 mL) was added hydrogen peroxide (30% solution, 99 mL, 1.0 mol), and the reaction mixture was stirred at 20 °C for 2 hours. It was then partitioned between water (200 mL) and dichloromethane (200 mL); the aqueous layer was extracted with dichloromethane (2 x 100 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Silica gel chromatography (Eluent: 10% ethyl acetate in petroleum ether) provided the product (30 g, which by 1H NMR analysis consisted of a 1 : 0.3 molar ratio of product and ethyl acetate) as a yellow oil. Corrected yield: 26 g, 130 mol, 67% over 2 steps. LCMS m/z 195.0 [M+H]+. 1H NMR (400 MHz, CDCl3), product peaks only: δ 6.98-7.05 (m, 2H), 6.94 (br d, half of AB quartet, J=9 Hz, 1H) 5.54 (br d, J=3.3 Hz, 1H).

A mixture of **C24** (9.5 g, 48 mmol) and **N**-iodosuccinimide (12 g, 53 mmol) in **N,N**-dimethylformamide (50 mL) was stirred at 25 °C for 4 hours, whereupon it was diluted with water (300 mL) and extracted with tert-butyl methyl ether (3 x 100 mL). The combined organic layers were washed sequentially with saturated aqueous sodium hydrogen sulfite solution (50 mL) and saturated aqueous sodium chloride solution (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (Gradient: 0% to 20% ethyl acetate in petroleum ether) afforded the product as a yellow oil. Yield: 12.0 g, 37.3 mmol, 78%. LCMS m/z 320.9 [M-H]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.40 (br s, 1H), 7.06 (dd, \(J=10.2, 2.0\) Hz, 1H), 5.78 (br s, 1H).

**Step 4. Synthesis of 2-[[benzyloxy]methoxy]-1-fluoro-3-iodo-5-(trifluoromethoxy)benzene (C26).**

Benzylic chloromethyl ether (7.66 g, 48.9 mmol) was added to a mixture of **C25** (10.5 g, 32.6 mmol) and potassium carbonate (9.01 g, 65.2 mmol) in acetonitrile (100 mL), and the resulting suspension was stirred at 25 °C for 2 hours. The reaction mixture was then diluted with water (400 mL) and extracted with dichloromethane (3 x 200 mL); the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 20% ethyl acetate in petroleum ether) provided the product as a colorless oil. Yield: 12.3 g, 27.8 mmol, 85%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.46-7.51 (m, 1H), 7.30-7.41 (m, 5H), 7.06 (ddq, \(J=10.9, 2.8, 0.7\) Hz, 1H), 5.33 (s, 2H), 4.93 (s, 2H).

**Step 5. Synthesis of 2-[[benzyloxy]methoxy]-1-fluoro-3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)benzene (C27).**

A mixture of **C26** (12.0 g, 27.1 mmol), but-2-ynoic acid (4.56 g, 54.2 mmol), and cesium carbonate (13.3 g, 40.8 mmol) in toluene (200 mL) was treated with allylpalladium chloride dimer (497 mg, 1.36 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (785 mg, 1.36 mmol). The reaction mixture was degassed twice with nitrogen, whereupon it was heated to 80 °C for 16 hours, then filtered through diatomaceous earth. The filtrate was concentrated in vacuo and purified by silica gel chromatography (Gradient: 0% to 30% ethyl acetate in petroleum ether), affording the product as a yellow oil. Yield: 9.2 g, 26 mmol, 96%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.40 (m, 5H), 7.05-7.09 (m, 1H), 6.96 (br dd, \(J=10.7, 2.6\) Hz, 1H), 5.35 (s, 2H), 4.91 (s, 2H), 2.07 (s, 3H).

Di-mu-chloro-dichlorobis(ethylene)diplatinum(II) (840 mg, 1.43 mmol) was added to a solution of C27 (9.2 g, 26 mmol) in toluene (200 mL); the reaction mixture was stirred at 35 °C for 16 hours, then allowed to stand at 25 °C for 2 days. The reaction mixture was concentrated in vacuo, and the residue was purified via silica gel chromatography (Gradient: 0% to 20% ethyl acetate in petroleum ether) to afford the product as a yellow oil. Yield: 6.5 g, 18 mmol, 69%. 1H NMR (400 MHz, CDCl₃) δ 7.30-7.41 (m, 5H), 7.19-7.23 (m, 1H), 6.91 (br d, J=10.5 Hz, 1H), 4.59 (s, 2H), 4.56 (s, 2H), 2.46 (s, 3H).


To a solution of C28 (3.0 g, 8.5 mmol) in ethanol (150 mL) was added palladium hydroxide on carbon (300 mg), and the reaction mixture was degassed three times with hydrogen. The resulting black suspension was stirred at 60 °C for 16 hours under 50 psi of hydrogen, whereupon it was filtered through diatomaceous earth. The filtrate was concentrated in vacuo; the residue was combined with material from a second reaction (carried out on 3.0 g of C28, 8.5 mmol) and subjected to chromatography on silica gel (Gradient: 0% to 50% ethyl acetate in petroleum ether), affording the product as a white solid. Yield: 3.60 g, 13.6 mmol, 80%. 1H NMR (400 MHz, CDCl₃) δ 7.28-7.31 (m, 1H), 6.92 (br d, J=10.7 Hz, 1H), 4.77 (br s, 2H), 2.52 (s, 3H).


Diiodomethane (43.8 g, 164 mmol) and diethylzinc (1 M solution in toluene, 81.8 mmol, 81.8 mL) were added to a solution of C29 (2.70 g, 10.2 mmol) in toluene (200 mL), and the reaction mixture was stirred at 30 °C for 16 hours. It was then added drop-wise to water (200 mL) at 0 °C; the resulting mixture was stirred for 10 minutes, whereupon it was filtered through diatomaceous earth. The aqueous layer was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Chromatography on silica gel (Gradient: 0% to 30% ethyl acetate in petroleum ether) provided the product as a yellow oil. Yield: 2.0 g, 7.2 mmol, 71%. LCMS m/z 261.0 [M-OH]^+. 1H NMR (400 MHz, CDCl₃) δ 7.10-7.12 (m, 1H), 6.85 (br d,
\[ J = 10.5 \text{ Hz, 1H}, 4.12 \text{ (d, } J = 12.0 \text{ Hz, 1H}), 3.87 \text{ (d, } J = 12.0 \text{ Hz, 1H}), 1.80 \text{ (s, 3H), 1.14 \text{ (d, } J = 6.5 \text{ Hz, 1H}), 0.70 \text{ (d, } J = 6.5 \text{ Hz, 1H}). \]

**Step 9. Synthesis of 2-[[3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl]-1H-isoindole-1,3(2H)-dione (C31).**

Diisopropyl azodicarboxylate (640 mg, 3.16 mmol) was added drop-wise to a mixture of C30 (800 mg, 2.88 mmol), 1H-isoindole-1,3(2H)-dione (465 mg, 3.16 mmol), and triphenylphosphine (830 mg, 3.16 mmol) in tetrahydrofuran (60 mL). The reaction mixture was stirred at 25 °C for 20 hours, whereupon it was concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 20% ethyl acetate in petroleum ether) provided the product as a colorless oil. Yield: 880 mg, 2.16 mmol, 75%. \(^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 7.86-7.91 \text{ (m, 2H), 7.73-7.78 \text{ (m, 2H), 7.46-7.49 \text{ (m, 1H), 6.81 \text{ (br d, } J = 10.3 \text{ Hz, 1H), 4.24 \text{ (d, } J = 15.2 \text{ Hz, 1H), 3.97 \text{ (d, } J = 15.3 \text{ Hz, 1H), 1.96 \text{ (s, 3H), 1.19 \text{ (d, } J = 6.6 \text{ Hz, 1H), 0.61 \text{ (d, } J = 6.8 \text{ Hz, 1H}).}}\]

**Step 10. Synthesis of 1-[[3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl]methanamine (C32).**

To a solution of C31 (500 mg, 1.2 mmol) in methanol (30 mL) was added hydrazine monohydrate (50% aqueous solution, 5 mL, 50 mmol), and the reaction mixture was stirred at 25 °C for 16 hours. After solvent had been removed in vacuo, the residue was diluted with dichloromethane (5 mL) and filtered; the filtrate was concentrated under reduced pressure to afford the product as a colorless oil. Yield: 300 mg, 1.1 mmol, 92%. \(^1\text{H NMR (400 MHz, DMSO-d_6)} \delta 7.39-7.43 \text{ (m, 1H), 7.21 \text{ (br d, } J = 10.9 \text{ Hz, 1H), 3.15 \text{ (d, } J = 13.8 \text{ Hz, 1H), 2.80 \text{ (d, } J = 13.9 \text{ Hz, 1H), 1.71 \text{ (s, 3H), 1.17 \text{ (d, } J = 6.3 \text{ Hz, 1H), 0.50 \text{ (d, } J = 6.3 \text{ Hz, 1H).}}\]

**Step 11. Synthesis of 2-[[3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y]methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (C33).**

1,3,4,6,7,8-Hexahydro-2H-pyrimido[1,2-a]pyrimidine (191 mg, 1.37 mmol) was added to a suspension of C10 (252 mg, 1.03 mmol) and C32 (190 mg, 0.685 mmol) in N,N-dimethylformamide (5 mL), and the reaction mixture was stirred at 25 °C for 30 minutes. Ethyl trifluoroacetate (386 mg, 2.72 mmol) was then added drop-wise over 5 minutes at 25 °C, whereupon the reaction mixture was stirred at 60 °C for 1 hour, cooled, and combined with similar material derived from a second reaction (carried out on 42.2 mg of C32, 0.152 mmol). The mixture was diluted with aqueous
sodium hydroxide solution (1 M, 5 mL) and saturated aqueous sodium chloride solution (5 mL), and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in *vacuo*. Purification via silica gel chromatography (Gradient: 0% to 10% methanol in dichloromethane) provided the racemic product as a yellow gum. Yield: 180 mg, 0.357 mmol, 43%. LCMS *m/z* 505.2 [M+H]*. 1H NMR (400 MHz, CDCl₃) δ 8.22 (br s, 1H), 7.45 (d, J=7.6 Hz, 1H), 7.29 (d, J=7.8 Hz, 1H), 7.12 (br s, 1H), 7.04-7.08 (m, 1H), 6.85 (br d, J=10 Hz, 1H), 5.06 (d, J=15.2 Hz, 1H), 4.23 (dd, J=5.9, 5.6 Hz, 2H), 3.57 (ddd, half of ABXY pattern, J=13, 6, 5 Hz, 1H), 3.48 (ddd, half of ABXY pattern, J=13, 6, 6 Hz, 1H), 3.16 (d, J=15.2 Hz, 1H), 2.28 (d, J=1 Hz, 3H), 1.89 (s, 3H), 1.07 (d, J=6.8 Hz, 1H), 0.76 (d, J=6.6 Hz, 1H).

Step 12. Isolation of 2-{[(1aS,6bS)-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (4) and 2-{[(1aR,6bR)-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (5).

Racemate C33 (160 mg, 0.32 mmol) was separated into its component enantiomers using supercritical fluid chromatography [Column: Chiral Technologies Chiralpak AD, 10 μm; Mobile phase: 30% (methanol containing 0.1% ammonium hydroxide) in carbon dioxide]. The second-eluting enantiomer was 4, isolated as a white solid. Yield: 71 mg, 0.14 μmol, 44%. LCMS *m/z* 505.1 [M+H]*. Retention time: 7.68 minutes (Column: Chiral Technologies Chiralpak AD-H, 4.6 x 250 mm, 5 μm; Mobile phase A: carbon dioxide; Mobile phase B: methanol containing 0.05% diethylamine; Gradient: 5% to 40% B; Flow rate: 2.5 mL/minute). 1H NMR (400 MHz, CDCl₃) δ 8.22 (br s, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.29 (d, J=7.8 Hz, 1H), 7.12 (br s, 1H), 7.05-7.08 (m, 1H), 6.85 (br d, J=10.2 Hz, 1H), 5.05 (d, J=15.2 Hz, 1H), 4.23 (dd, J=6.2, 5.5 Hz, 2H), 3.57 (ddd, half of ABXY pattern, J=13, 5.5, 5.5 Hz, 1H), 3.48 (ddd, half of ABXY pattern, J=13, 6, 6 Hz, 1H), 3.17 (d, J=15.3 Hz, 1H), 2.28 (br s, 3H), 1.89 (s, 3H), 1.07 (d, J=6.8 Hz, 1H), 0.76 (d, J=6.6 Hz, 1H).

The first-eluting enantiomer, 5, was also obtained as a white solid. Yield: 73 mg, 0.14 μmol, 44%. LCMS *m/z* 505.2 [M+H]*. Retention time: 6.42 minutes, using the same analytical conditions as those reported above for 4. 1H NMR (400 MHz, CDCl₃) δ 8.21 (br s, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.29 (d, J=7.8 Hz, 1H), 7.12 (br s, 1H), 7.04-7.08 (m, 1H), 6.85 (br d, J=10.4 Hz, 1H), 5.06 (d, J=15.3 Hz, 1H), 4.23 (dd, J=6.0, 5.6 Hz, 2H), 3.57 (ddd, half of ABXY pattern, J=13, 5.5, 5.5 Hz, 1H), 3.48 (ddd, half of ABXY pattern, J=13, 6, 6 Hz, 1H), 3.16 (d, J=15.3 Hz, 1H), 2.28 (d, J=0.8 Hz, 3H), 1.89 (s, 3H), 1.07 (d, J=6.8 Hz, 1H), 0.76 (d, J=6.8 Hz, 1H).
Examples 6 and 7

2-[[((1aS,6bS)-4-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (6) and 2-[[((1aR,6bR)-4-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyridinol1,2-a]pyrazine-1,6-dione (7)
Step 1. Synthesis of 5-fluoro-2-iodo-4-(trifluoromethoxy)phenol (C34).

A mixture of 3-fluoro-4-(trifluoromethoxy)phenol (7.0 g, 36 mmol) and N-iodosuccinimide (95%, 8.45 g, 35.7 mmol) in acetic acid (10 mL) was stirred at room temperature for 5 minutes and then treated with concentrated sulfuric acid (18 M, 0.58 mL, 10.4 mmol). After the reaction mixture had stirred overnight, it was partitioned between water and diethyl ether. The organic layer was washed with water and with 2 M aqueous sodium thiosulfate solution, treated with activated carbon, and dried over magnesium sulfate. The mixture was filtered through a pad of diatomaceous earth and silica gel, and the filtrate was concentrated in vacuo, providing the product as an oil (11.0 g), which by $^1$H NMR analysis contained two molar equivalents of acetic acid. Yield, corrected for acetic acid: 8.0 g, 25 mmol, 70%. GCMS $m/z$ 322.0 [M$^+$]. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.60 (br d, $J$=8.1 Hz, 1H), 6.88 (d, $J$=10.9 Hz, 1H).


A mixture of C34 [from the previous step; 11.0 g (corrected for acetic acid: 8.0 g, 25 mmol)], ethyl but-2-ynoate (4.0 mL, 34 mmol), and potassium carbonate (18.0 g, 130 mmol) in acetonitrile (100 mL) was heated at reflux for 6 hours, then allowed to stir at room temperature overnight. After the reaction mixture had been partitioned between water and diethyl ether, the organic layer was
washed with water and with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (Gradient: 0% to 5% ethyl acetate in heptane) provided the product as an oil. Yield: 8.60 g, 19.8 mmol, 79%. GCMS m/z 434.1 [M+]. 1H NMR (400 MHz, CDCl₃) δ 7.78 (br d, J=8.0 Hz, 1H), 6.98 (d, J=10.0 Hz, 1H), 4.78 (s, 1H), 4.13 (q, J=7.1 Hz, 2H), 2.53 (s, 3H), 1.25 (t, J=7.1 Hz, 3H).


A stream of nitrogen was bubbled through a solution of C35 (250 mg, 0.576 mmol) in acetonitrile (5 mL) for 10 minutes, whereupon triethylamine (0.40 mL, 2.9 mmol) was added to the solution, followed by bis(tri-tert-butylphosphine)palladium(0) (14.9 mg, 29.2 µmol). The reaction mixture was heated to 90 °C for 20 hours, cooled to room temperature, and partitioned between diethyl ether and water. The organic layer was washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure; silica gel chromatography (Gradient: 0% to 5% ethyl acetate in heptane) provided the product as a white solid. Yield: 148 mg, 0.483 mmol, 84%. 1H NMR (400 MHz, CDCl₃) δ 7.91 (dq, J=7.7, 1.1 Hz, 1H), 7.30 (d, J=9.3 Hz, 1H), 4.43 (q, J=7.1 Hz, 2H), 2.78 (s, 3H), 1.45 (t, J=7.1 Hz, 3H).

Step 4. Synthesis of 4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-carboxylic acid (C37).

A suspension of trimethylsulfoxonium iodide (98%, 1.35 g, 6.01 mmol) in dimethyl sulfoxide (10 mL) was treated with potassium tert-butoxide (645 mg, 5.75 mmol) and stirred at room temperature for 30 minutes. A solution of C36 (1.60 g, 5.22 mmol) in dimethyl sulfoxide (5 mL) and tetrahydrofuran (2 mL) was added; the reaction mixture was stirred for 2 hours, whereupon it was treated with additional trimethylsulfoxonium iodide (98%, 300 mg, 1.3 mmol) and potassium tert-butoxide (130 mg, 1.16 mmol). After 30 minutes, potassium hydroxide (85%, 700 mg, 11 mmol) was added, and stirring was continued for 2 hours. Water (10 mL) was added to the reaction mixture, which was then adjusted to a pH of 4 – 5 via addition of 1 M aqueous hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were washed with water and with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting thick oil was treated with heptane (100 mL), concentrated under reduced pressure, dissolved in diethyl ether, washed twice with water, dried over sodium sulfate, filtered, and concentrated in vacuo. The product was obtained as a solid.
Yield: 1.40 g, 4.79 mmol, 92%. $^1$H NMR (400 MHz, CD$_3$OD) δ 7.57 (br d, J=7.9 Hz, 1H), 6.83 (d, J=10.4 Hz, 1H), 1.98 (d, J=6.2 Hz, 1H), 1.83 (s, 3H), 0.92 (d, J=6.3 Hz, 1H).

**Step 5. Synthesis of 4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-carboxamide (C38).**

1,1'-Carbonyldimidazole (266 mg, 1.64 mmol) was added to a solution of C37 (400 mg, 1.37 mmol) in tetrahydrofuran (10 mL), and the reaction mixture was stirred at room temperature for 30 minutes. Concentrated ammonium hydroxide solution (0.7 mL) was added, and stirring was continued for 1 hour, whereupon the reaction mixture was partitioned between water and diethyl ether. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated in vacuo, providing the product as a pasty solid. Yield: 390 mg, 1.34 mmol, 98%. GCMS m/z 291.2 [M$^+$$^\cdot$]. $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.50 (br d, J=7.9 Hz, 1H), 7.41 (br s, 1H), 7.31 (br s, 1H), 7.15 (d, J=10.9 Hz, 1H), 1.96 (d, J=6.6 Hz, 1H), 1.65 (s, 3H), 0.75 (d, J=6.6 Hz, 1H).

**Step 6. Synthesis of 1-[4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methanamine (C39).**

Sodium bis(2-methoxyethoxy)aluminum hydride (3.3 M solution in toluene; 7.0 mL, 23 mmol) was added to a solution of C38 (1.70 g, 5.84 mmol) in toluene (30 mL). The reaction mixture was stirred at room temperature for 2 hours, whereupon it was cooled in an ice bath and quenched with aqueous sodium hydroxide solution (1 M, 30 mL). The resulting mixture was extracted with diethyl ether; the combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 5% methanol in dichloromethane) afforded the product as a thick oil. Yield: 1.2 g, 4.3 mmol, 74%. GCMS m/z 260.2 [M$+$NH$_3$]$^\cdot$.$^1$H NMR (400 MHz, CDCl$_3$) δ 7.25-7.31 (m, 1H, assumed; partially obscured by solvent peak), 6.66 (d, J=10.2 Hz, 1H), 3.34 (d, J=14.0 Hz, 1H), 2.87 (d, J=14.0 Hz, 1H), 1.75 (s, 3H), 0.95 (d, J=6.3 Hz, 1H), 0.56 (d, J=6.3 Hz, 1H).

**Step 7. Synthesis of 2-{[4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (C40).**

Conversion of C39 to the product was carried out using the method described for synthesis of C22 from C21 in Examples 2 and 3. The product was obtained as a white solid. Yield: 560 mg, -78-.
1.11 mmol, 97%. LCMS m/z 505.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, J=1.2 Hz, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.24-7.31 (m, 2H, assumed; partially obscured by solvent peak), 7.11-7.14 (m, 1H), 6.68 (d, J=10.0 Hz, 1H), 5.06 (d, J=15.1 Hz, 1H), 4.26 (ddd, half of ABXY pattern, J=14.2, 6.3, 4.7 Hz, 1H), 4.20 (ddd, half of ABXY pattern, J=14.3, 8.0, 4.4 Hz, 1H), 3.56 (ddd, half of ABXY pattern, J=13.2, 6.3, 4.5 Hz, 1H), 3.46 (ddd, half of ABXY pattern, J=13.2, 7.9, 4.5 Hz, 1H), 3.12 (d, J=15.2 Hz, 1H), 2.29 (br s, 3H), 1.84 (s, 3H), 1.00 (d, J=6.6 Hz, 1H), 0.68 (d, J=6.6 Hz, 1H).

Step 8. Isolation of 2-[[1aS,6bS]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (6) and 2-[[1aR,6bR]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (7).

Separation of C40 (560 mg, 1.1 mmol) into its component enantiomers was carried out via supercritical fluid chromatography [Column: Chiral Technologies Chiralpak AD-H, 5 μm; Mobile phase: 30% (0.2% ammonium hydroxide in methanol) in carbon dioxide]. Each enantiomer was then dissolved in ethyl acetate (15 mL), filtered, and concentrated in vacuo; suspension in diethyl ether followed by filtration provided the products, both as solids. Compound 6 was the second-eluting enantiomer. Yield: 160 mg, 0.317 mg, 28%. LCMS m/z 505.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.26-7.31 (m, 2H, assumed; partially obscured by solvent peak), 7.13 (br s, 1H), 6.68 (d, J=10.0 Hz, 1H), 5.06 (d, J=15.2 Hz, 1H), 4.26 (ddd, half of ABXY pattern, J=14, 6, 5 Hz, 1H), 4.20 (ddd, half of ABXY pattern, J=14, 8, 4 Hz, 1H), 3.56 (ddd, half of ABXY pattern, J=13, 6, 5 Hz, 1H), 3.46 (ddd, half of ABXY pattern, J=13, 8, 5 Hz, 1H), 3.12 (d, J=15.2 Hz, 1H), 2.29 (s, 3H), 1.84 (s, 3H), 1.00 (d, J=6.6 Hz, 1H), 0.68 (d, J=6.6 Hz, 1H).

Compound 7 was the first-eluting enantiomer. Yield: 180 mg, 0.357 mmol, 31%. LCMS m/z 505.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.26-7.31 (m, 2H, assumed; partially obscured by solvent peak), 7.13 (br s, 1H), 6.68 (d, J=10.0 Hz, 1H), 5.06 (d, J=15.2 Hz, 1H), 4.26 (ddd, half of ABXY pattern, J=14.5, 6, 5 Hz, 1H), 4.20 (ddd, half of ABXY pattern, J=14.3, 7.8, 4.3 Hz, 1H), 3.56 (ddd, half of ABXY pattern, J=13, 6, 4.5 Hz, 1H), 3.46 (ddd, half of ABXY pattern, J=13, 8, 5 Hz, 1H), 3.12 (d, J=15.1 Hz, 1H), 2.29 (s, 3H), 1.84 (s, 3H), 1.00 (d, J=6.6 Hz, 1H), 0.68 (d, J=6.6 Hz, 1H).
Examples 8 and 9

2-[[1aS,6bS]-4-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-
pyrido[1,2-a]pyrazine-1,6-dione (8) and 2-[[1aR,6bR]-4-Fluoro-1a-methyl-5-(trifluoromethoxy)-
1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-
dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (9)

\[
\begin{align*}
\text{C41} & \xrightarrow{\text{Br}_2} \text{C42} \\
\text{C39} & \xrightarrow{\text{C42}} \text{C43} \\
\text{C43} & \xrightarrow{\text{Pd}_2(\text{dba})_3, \text{K}_3\text{PO}_4} \text{C44}
\end{align*}
\]

Step 1. Synthesis of 5-bromo-6-oxo-1,6-dihydropyridine-2-carboxylic acid (C41).

Bromine (115 g, 720 mmol) was added drop-wise to a suspension of 6-oxo-1,6-
dihydropyridine-2-carboxylic acid (25 g, 180 mmol) in acetic acid (400 mL). The reaction mixture
was heated to 80 °C for 16 hours, whereupon it was concentrated to dryness under reduced
pressure. The residue was triturated with tert-butyl methyl ether (200 mL) and filtered; the filter cake
was washed with tert-butyl methyl ether (3 x 100 mL) to provide the product as a gray solid. Yield:
39.0 g, 179 mmol, 99%. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.03 (d, \(J=7.3\) Hz, 1H), 6.83 (d, \(J=7.3\) Hz, 1H).
Step 2. Synthesis of 7-bromo-3,4-dihydropyrida[2,1-c][1,4]oxazine-1,6-dione (C42).

This transformation was carried out in four identical batches. 1,2-Dibromoethane (9.48 g, 50.5 mmol) was added to a suspension of C41 (10.0 g, 45.9 mmol) and cesium carbonate (37.4 g, 115 mmol) in N,N-dimethylformamide (50 mL). The reaction mixture was stirred at 95 °C for 2 hours, whereupon it was cooled to about 30 °C and combined with the other three batches. This material was poured into dichloromethane (600 mL) and stirred at room temperature for 10 minutes, then filtered. The filter cake was washed with dichloromethane (200 mL), and the combined filtrates were concentrated to dryness under reduced pressure. The residue was mixed with dichloromethane (100 mL), stirred at 25 °C for 20 minutes, and then filtered. The collected solid was dissolved in a mixture of dichloromethane (500 mL) and methanol (30 mL), and filtered through silica gel (10 g). This filtrate was concentrated in vacuo and triturated with a mixture of dichloromethane (50 mL) and tert-butyl methyl ether (50 mL), affording the product as a pale yellow solid. Yield: 13 g, 53 mmol, 29%. LCMS m/z 245.8 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 7.91 (d, J=7.5 Hz, 1H), 7.14 (d, J=7.5 Hz, 1H), 4.64 (dd, J=5.3, 5.1 Hz, 2H), 4.36 (dd, J=5.3, 5.1 Hz, 2H).

Step 3. Synthesis of 7-bromo-2-[[4-fluoro-1-ethyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (C43).

1,3,4,6,7,8-Hexahydro-2H-pyrimido[1,2-a]pyrimidine (97%, 932 mg, 6.49 mmol) was added to a mixture of C39 (1.20 g, 4.33 mmol) and C42 (1.37 g, 5.61 mmol) in N,N-dimethylformamide (5 mL). The reaction mixture was stirred at room temperature for 2 hours, then treated with ethyl trifluoroacetate (1.3 mL, 10.9 mmol). After 1 hour, aqueous sodium hydroxide solution (1 M, 10 mL) was added, and stirring was continued for 15 minutes. The mixture was then extracted with ethyl acetate, and the combined organic layers were washed with water, dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (Gradient: 30% to 100% ethyl acetate in heptane) provided the product as an oil. Yield: 1.76 g, 3.50 mmol, 81%. LCMS m/z 503.3, 505.3 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 7.86 (d, J=7.6 Hz, 1H), 7.24-7.28 (m, 1H, assumed; partially obscured by solvent peak), 7.07 (d, J=7.6 Hz, 1H), 6.67 (d, J=9.9 Hz, 1H), 5.01 (d, J=15.2 Hz, 1H), 4.18 (dd, J=6.0, 5.8 Hz, 2H), 3.52 (ddd, half of ABXY pattern, J=13, 5.5, 5.5 Hz, 1H), 3.42 (ddd, half of ABXY pattern, J=13, 6, 6 Hz, 1H), 3.11 (d, J=15.2 Hz, 1H), 1.82 (s, 3H), 0.98 (d, J=6.6 Hz, 1H), 0.67 (d, J=6.6 Hz, 1H).
Step 4. Synthesis of 2-[[4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (C44).

A mixture of tris(dibenzylideneacetone)dipalladium(0) (98%, 94.7 mg, 0.101 mmol) and di-tert-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (95%, 103 mg, 0.203 mmol) in toluene (10 mL) was degassed with nitrogen for 5 minutes, then heated at 125 °C for 3 minutes. In a separate flask, a mixture of C43 (1.70 g, 3.38 mmol), 3-methyl-1H-1,2,4-triazole (561 mg, 6.75 mmol), and potassium phosphate (1.48 g, 6.97 mmol) in toluene (10 mL) and 1,4-dioxane (10 mL) was degassed with nitrogen for 10 minutes. The catalyst solution was transferred to the reaction flask via syringe, and the reaction mixture was heated at 125 °C for 2 hours, whereupon it was partitioned between water and ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo; silica gel chromatography (Gradient: 50% to 100% ethyl acetate in heptane) provided the product as an off-white solid. Yield: 1.3 g, 2.6 mmol, 77%. LCMS m/z 506.4 [M+H]+. 1H NMR (400 MHz, CDCl₃), characteristic peaks: δ 9.52 (br s, 1H), 8.21 (d, J=7.9 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.25-7.31 (m, 1H, assumed; partially obscured by solvent peak), 6.68 (d, J=10.0 Hz, 1H), 5.05 (d, J=15.2 Hz, 1H), 4.20-4.32 (m, 2H), 3.53-3.62 (m, 1H), 3.14 (d, J=15.2 Hz, 1H), 2.49 (s, 3H), 1.84 (s, 3H), 1.00 (d, J=6.6 Hz, 1H), 0.69 (d, J=6.5 Hz, 1H).

Step 5. Isolation of 2-[[1aS,6bS]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (8) and 2-[[1aR,6bR]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (9).

Compound C44 (1.3 g, 2.6 mmol) was separated into its component enantiomers via supercritical fluid chromatography [Column: Phenomenex Lux Cellulose-4, 5 μm; Mobile phase: 30% (1:1 acetonitrile / methanol) in carbon dioxide]. The individual enantiomers from the separation were dissolved in ethyl acetate (10 mL), passed through a syringe filter, concentrated in vacuo, and then precipitated with diethyl ether; both enantiomers were obtained as solids. Example 8 was the second-eluting enantiomer. Yield: 415 mg, 0.821 mmol, 32%. LCMS m/z 506.4 [M+H]+. 1H NMR (400 MHz, CDCl₃) δ 9.53 (br s, 1H), 8.21 (d, J=7.9 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.29 (dq, J=7.5, 1.0 Hz, 1H), 6.68 (d, J=10.0 Hz, 1H), 5.05 (d, J=15.2 Hz, 1H), 4.20-4.32 (m, 2H), 3.57 (ddd, half of ABXY pattern, J=13.2, 6.0, 4.9 Hz, 1H), 3.44-3.51 (m, 1H), 3.14 (d, J=15.2 Hz, 1H), 2.48 (s, 3H), 1.84 (s, 3H), 1.00 (d, J=6.6 Hz, 1H), 0.69 (d, J=6.6 Hz, 1H).
The first-eluting enantiomer was compound 9. Yield: 412 mg, 0.815 mmol, 31%. LCMS m/z 506.4 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 9.52 (br s, 1H), 8.21 (d, J=7.9 Hz, 1H), 7.38 (d, J=7.9 Hz, 1H), 7.28 (dq, J=7.6, 1.0 Hz, 1H), 6.68 (d, J=10.0 Hz, 1H), 5.05 (d, J=15.2 Hz, 1H), 4.20-4.32 (m, 2H), 3.57 (ddd, half of ABXY pattern, J=13.2, 6.0, 4.9 Hz, 1H), 3.44-3.51 (m, 1H), 3.14 (d, J=15.2 Hz, 1H), 2.49 (s, 3H), 1.84 (s, 3H), 1.00 (d, J=6.6 Hz, 1H), 0.69 (d, J=6.7 Hz, 1H).

Examples 10 and 11

2-[[1aS,6bS)-4-Chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y1[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (10)

and 2-[[1aR,6bR)-4-Chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-y1[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (11)
Step 1. Synthesis of 5-chloro-2-iodo-4-(trifluoromethyl)phenol (C45).

A mixture of 3-chloro-4-(trifluoromethyl)phenol (3.00 g, 15.3 mmol) and N-iodosuccinimide (95%, 3.61 g, 15.2 mmol) in acetic acid (10 mL) was stirred for 5 minutes, whereupon sulfuric acid (18 M, 0.25 mL, 4.5 mmol) was added. After the reaction mixture had been stirred at room temperature for 2 days, it was partitioned between diethyl ether and water. The organic layer was washed with water and with 2 M aqueous sodium thiosulfate solution, then treated with activated carbon and dried over magnesium sulfate. The mixture was filtered through a pad of diatomaceous earth and silica gel, and the filtrate was concentrated in vacuo to afford an oil (4.9 g) containing product, acetic acid, and solvent. This material was taken into the following step without additional purification. GCMS m/z 322.0 [M⁺]. ¹H NMR (400 MHz, CDCl₃), product peaks only: δ 7.95 (s, 1H), 7.12 (s, 1H).


A mixture of C45 (from the previous step; 4.9 g, ≤15.3 mmol) and potassium carbonate (10.5 g, 76.0 mmol) in acetonitrile (100 mL) was stirred for 10 minutes. Ethyl but-2-ynoate (2.0 mL, 17 mmol) was added, and the reaction mixture was heated at reflux overnight; GCMS analysis indicated partial conversion to product. The reaction mixture was partitioned between 1 M aqueous hydrochloric acid and a 1:1 mixture of diethyl ether and heptane. The organic layer was washed with water and with saturated aqueous sodium chloride solution, then dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 25% ethyl acetate in heptane) afforded recovered C45 (2.84 g) and a mixture of product and the des-ido analogue (0.88 g). The recovered C45 was resubjected to the reaction conditions and worked up in the same manner, affording the product (1.2 g) as a thick oil that slowly solidified, and recovered C45 (1.6 g). A portion of this C45 (1.2 g, 3.7 mmol) was dissolved in toluene (10 mL) and treated with 1,4-
diazabicyclo[2.2.2]octane (411 mg, 3.66 mmol), followed by ethyl but-2-ynoate (1 mL, 9 mmol). The reaction mixture was heated at 100 °C for 18 hours, then cooled to room temperature and combined with the 0.88 g of material isolated above. This mixture was partitioned between diethyl ether and 1 M aqueous hydrochloric acid; the organic layer was washed with 1 M aqueous hydrochloric acid and with water, then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Chromatography on silica gel (Gradient: 0% to 5% ethyl acetate in heptane) afforded additional product (2.0 g) as an oil. Combined yield: 3.2 g, 7.4 mmol, 48% over 2 steps. GCMS m/z 434.1 [M+]. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.20 (br s, 1H), 4.80-4.82 (m, 1H), 4.14 (q, J=7.1 Hz, 2H), 2.54 (d, J=0.6 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H).


A solution of C46 (3.10 g, 7.13 mmol) in acetonitrile (20 mL) was purged with nitrogen for 10 minutes, then treated with triethylamine (5.0 mL, 36 mmol), followed by bis(tri-tert-butylphosphine)palladium(0) (184 mg, 0.360 mmol). The reaction mixture was heated at 90 °C for 1 hour, whereupon it was partitioned between diethyl ether and 1 M aqueous hydrochloric acid. The organic layer was washed with water and with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and treated with activated carbon. The mixture was filtered through a pad of diatomaceous earth, and the filtrate was concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 5% ethyl acetate in heptane) afforded the product as an off-white / tan solid. Yield: 1.00 g, 3.26 mmol, 46%. GCMS m/z 306.1 [M+]. ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.60 (s, 1H), 4.44 (q, J=7.1 Hz, 2H), 2.80 (s, 3H), 1.46 (t, J=7.1 Hz, 3H).

Step 4. Synthesis of 4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-carboxylic acid (C48).

A suspension of trimethylsulfoxonium iodide (98%, 820 mg, 3.7 mmol) in dimethyl sulfoxide (5 mL) was treated with potassium tert-butoxide (1 M solution in tetrahydrofuran; 3.59 mL, 3.59 mmol) and allowed to stir at room temperature for 20 minutes. A solution of C47 (1.00 g, 3.26 mmol) in dimethyl sulfoxide (5 mL) and tetrahydrofuran (3 mL) was added, and stirring was continued for 1.5 hours. At this point, additional trimethylsulfoxonium iodide (98%, 125 mg, 0.557 mmol) and potassium tert-butoxide (1 M solution in tetrahydrofuran; 0.5 mL, 0.5 mmol) were introduced, and the reaction was allowed to proceed for 1.5 hours. Crushed potassium hydroxide pellets (85%, 540 mg, 8.2 mmol) were added, and the reaction mixture was stirred for 2 hours; it
was then adjusted to a pH of 4 – 5 via addition of 1 M aqueous hydrochloric acid. The mixture was extracted with ethyl acetate, and the combined organic layers were washed with water and with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo to afford the product as a pasty solid (1.16 g); this material was impure by $^1$H NMR analysis, and was used in the following step without further purification. $^1$H NMR (400 MHz, DMSO-$d_6$), product peaks only: $\delta$ 13.2-13.4 (v br s, 1H), 7.94 (s, 1H), 7.35 (s, 1H), 1.97 (d, $J$=6.4 Hz, 1H), 1.80 (s, 3H), 1.07 (d, $J$=6.4 Hz, 1H).

Step 5. Synthesis of 4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-carboxamide (C49).

Conversion of C48 (from the previous step; 1.10 g, $\leq$3.1 mmol) to the product was carried out according to the method described for synthesis of C38 from C37 in Examples 6 and 7. The product was isolated as a thick oil (1.1 g), which was impure by $^1$H NMR analysis; this material was taken to the next step without additional purification. GCMS m/z 291.1 [M$^+$]. $^1$H NMR (400 MHz, DMSO-$d_6$), product peaks only: $\delta$ 7.76 (s, 1H), 7.33 (s, 1H), 2.03 (d, $J$=6.6 Hz, 1H), 1.68 (s, 3H), 0.79 (d, $J$=6.6 Hz, 1H).

Step 6. Synthesis of 1-[4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methanamine (C50).

Sodium bis(2-methoxyethoxy)aluminum hydride (3.3 M solution in toluene; 4.2 mL, 13.9 mmol) was added to a solution of C49 (from the previous step; 1.0 g, $\leq$2.8 mmol) in toluene (25 mL) and tetrahydrofuran (5 mL). After 2 hours at room temperature, the reaction mixture was cooled in an ice bath, quenched with aqueous sodium hydroxide solution (1 M, 25 mL, 25 mmol), and extracted with diethyl ether. The organic layer was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo, affording the product as a thick gum (865 mg). By $^1$H NMR analysis, this material was impure; it was used in the following step without additional purification. $^1$H NMR (400 MHz, CDCl$_3$), product peaks only: $\delta$ 7.66 (s, 1H), 6.94 (s, 1H), 3.39 (d, $J$=14.0 Hz, 1H), 2.89 (d, $J$=14.1 Hz, 1H), 1.77 (s, 3H), 1.01 (d, $J$=6.4 Hz, 1H), 0.54 (d, $J$=6.3 Hz, 1H).

Step 7. Synthesis of 2-[[1aS,6bS]-4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (10) and 2-[[1aR,6bR]-4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-
6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (11).

1,3,4,6,7,8-Hexahydro-2H-pyrimido[1,2-a]pyrimidine (97%, 671 mg, 4.68 mmol) was added to a mixture of C50 (from the previous step; 865 mg, ≤2.8 mmol) and C10 (993 mg, 4.05 mmol) in N,N-dimethylformamide (5 mL). After 2 hours, ethyl trifluoroacetate (0.93 mL, 7.8 mmol) was added to the reaction mixture, and stirring was continued for 1 hour. Aqueous sodium hydroxide solution (1 M, 10 mL, 10 mmol) was added and the mixture was stirred for 15 minutes, whereupon it was partitioned between water and ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated in vacuo. After the residue had been purified via chromatography on silica gel (Gradient: 0% to 10% methanol in ethyl acetate), it was triturated with diethyl ether, and the resulting solid (470 mg) was separated into its component enantiomers via supercritical fluid chromatography [Column: Chiral Technologies Chiralpak AD-H, 5 μm; Mobile phase: 20% (1:1 acetonitrile / methanol) in carbon dioxide]. Each enantiomer was then dissolved in ethyl acetate (10 mL) and passed through a syringe filter. The eluents were concentrated in vacuo and triturated with diethyl ether, to afford each product as a solid.

Compound 10 was the second-eluting enantiomer. Yield: 114 mg, 0.226 mmol, 8% over 4 steps. LCMS m/z 505.4, 507.4 [M+H]+. 1H NMR (400 MHz, CD3OD) δ 8.31 (br s, 1H), 7.79 (s, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.31 (br s, 1H), 7.27 (d, J=7.8 Hz, 1H), 7.04 (s, 1H), 4.85 (d, J=15.1 Hz, 1H), 4.33 (ddd, half of ABXY pattern, J=14, 6, 4 Hz, 1H), 4.19 (ddd, half of ABXY pattern, J=14, 9, 4 Hz, 1H), 3.73 (ddd, half of ABXY pattern, J=13, 6, 4 Hz, 1H), 3.5-3.58 (m, 1H), 3.50 (d, J=15.3 Hz, 1H), 2.23 (br s, 3H), 1.87 (s, 3H), 1.23 (d, J=6.8 Hz, 1H), 0.63 (d, J=6.7 Hz, 1H).

The first-eluting enantiomer was 11. Yield: 122 mg, 0.242 mmol, 9% over 4 steps. LCMS m/z 505.4, 507.3 [M+H]+. 1H NMR (400 MHz, CD3OD) δ 8.30 (br s, 1H), 7.79 (s, 1H), 7.77 (d, J=7.7 Hz, 1H), 7.30 (br s, 1H), 7.27 (d, J=7.7 Hz, 1H), 7.04 (s, 1H), 4.85 (d, J=15.2 Hz, 1H), 4.33 (ddd, half of ABXY pattern, J=14, 6, 4 Hz, 1H), 4.19 (ddd, half of ABXY pattern, J=14, 9, 4 Hz, 1H), 3.73 (ddd, half of ABXY pattern, J=13, 6, 4 Hz, 1H), 3.54 (ddd, half of ABXY pattern, J=13, 9, 4 Hz, 1H), 3.50 (d, J=15.3 Hz, 1H), 2.23 (d, J=0.8 Hz, 3H), 1.87 (s, 3H), 1.23 (d, J=6.8 Hz, 1H), 0.63 (d, J=6.6 Hz, 1H).

Examples 12 and 13

2-((((1aS,6bS)-5-(Difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (12) and 2-((((1aR,6bR)-5-(Difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-
Step 1. Synthesis of 4-bromo-1-(difluoromethoxy)-2-fluorobenzene (C51).

4-Bromo-2-fluorophenol (2.78 mL, 25.4 mmol) was added to a mixture of cesium carbonate (97%, 12.8 g, 38.1 mmol), N,N-dimethylformamide (100 mL), and water (10 mL) at 70 °C. Sodium chloro(difluoro)acetate (9.69 g, 63.6 mmol) was then introduced portion-wise, over 30 minutes. The reaction mixture was allowed to stir at 70 °C overnight, whereupon it was cooled to room temperature and poured into water. The resulting mixture was extracted three times with ethyl acetate; the combined organic layers were washed sequentially with 1 M aqueous sodium...
hydroxide solution, water, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 20% ethyl acetate in heptane) afforded the product as a colorless oil. Yield: 1.50 g, 6.22 mmol, 24%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36 (dd, \(J=9.7, 2.3\) Hz, 1H), 7.28 (ddd, \(J=8.7, 2.2, 1.6\) Hz, 1H), 7.14 (br dd, \(J=8.6, 8.4\) Hz, 1H), 6.54 (t, \(J_{HF}=73.0\) Hz, 1H).

Step 2. Synthesis of 4-(difluoromethoxy)-3-fluorophenol (C52).

A mixture of water (3 mL) and 1,4-dioxane (3 mL) was purged with nitrogen for 15 minutes, whereupon potassium hydroxide (85%, 1.64 g, 24.8 mmol), tris(dibenzylideneacetone)dipalladium(0) (57 mg, 62 mmol), and di-tert-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (97%, 123 mg, 0.248 mmol) were added. After addition of \(\textbf{C51}\) (1.50 g, 6.22 mmol), the reaction mixture was heated at 100 °C for 1 hour, then cooled to room temperature and treated with aqueous sodium hydroxide solution (1 M, 100 mL). The resulting mixture was washed with diethyl ether (50 mL), adjusted to acidic pH via addition of concentrated hydrochloric acid, and extracted with diethyl ether (2 x 150 mL). These extracts were combined, treated with decolorizing carbon, dried over magnesium sulfate, filtered, and concentrated in vacuo, affording the product (1.36 g) as an oil. This material contained significant solvent by \(^1\)H NMR analysis, and was taken to the following step without additional manipulation. \(^1\)H NMR (400 MHz, CDCl\(_3\)), product peaks only: \(\delta\) 7.08 (br dd, \(J=8.9, 8.9\) Hz, 1H), 6.65 (dd, \(J=11.6, 2.9\) Hz, 1H), 6.56 (ddd, \(J=8.9, 2.9, 1.5\) Hz, 1H), 6.45 (t, \(J_{HF}=73.9\) Hz, 1H).


A solution of \(\textbf{C52}\) (from the previous step; 1.36 g, \(\leq 6.22\) mmol; estimated to contain \(\sim 4.6\) mmol of \(\textbf{C52}\) from analysis of the \(^1\)H NMR spectrum) in dichloromethane (23 mL) was cooled in an ice bath and treated with bromine (0.24 mL, 4.6 mmol) in a drop-wise manner. The reaction mixture was allowed to warm slowly to room temperature overnight, whereupon it was washed with aqueous sodium thiosulfate solution, dried over magnesium sulfate, filtered, and concentrated in vacuo. The product was obtained as an oil (1.4 g), which contained solvent as judged by \(^1\)H NMR analysis; this material was used directly in the following step. GCMS \(m/z\) 256.0 [M\(^+\)]. \(^1\)H NMR (400 MHz, CDCl\(_3\)), product peaks only: \(\delta\) 7.40 (br d, \(J=7.9\) Hz, 1H), 6.88 (d, \(J=11.0\) Hz, 1H), 6.47 (t, \(J_{HF}=73.2\) Hz, 1H), 5.67-5.78 (br s, 1H).

1,4-Diazabicyclo[2.2.2]octane (589 mg, 5.25 mmol) was added to a solution of C53 (from the previous step; 1.4 g, estimated to contain ~4.3 mmol of C53 from analysis of the \(^1\)H NMR spectrum) and ethyl but-2-ynoate (0.90 mL, 7.7 mmol) in toluene (13 mL). The reaction mixture was heated at 90 °C for 6 hours, whereupon it was cooled to room temperature and partitioned between 1 M aqueous hydrochloric acid and diethyl ether. The organic layer was washed sequentially with 1 M aqueous hydrochloric acid, 1 M aqueous sodium hydroxide solution, and with water. It was then dried over magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (Gradient: 0% to 5% ethyl acetate in heptane) afforded the product as a thick oil. Yield: 1.23 g, 3.33 mmol, 54% over 3 steps. GCMS m/z 323, 325 [M−(OEt)]\(^+\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.55 (br d, \(J=7.9\) Hz, 1H), 6.99 (d, \(J=10.0\) Hz, 1H), 6.56 (t, \(J_{HF}=72.5\) Hz, 1H), 4.78 (s, 1H), 4.13 (q, \(J=7.1\) Hz, 2H), 2.52 (s, 3H), 1.25 (t, \(J=7.1\) Hz, 3H).

Step 5. Synthesis of ethyl 5-(difluoromethoxy)-6-fluoro-2-methyl-1-benzofuran-3-carboxylate (C55).

A solution of C54 (1.23 g, 3.33 mmol) and triethylamine (2.0 mL, 14 mmol) in acetonitrile (10 mL) was purged with nitrogen for 15 minutes. Bis(tri-tert-butylphosphine)palladium(0) (170 mg, 0.33 mmol) was introduced, and the reaction mixture was heated at 90 °C for 2 hours, whereupon it was cooled to room temperature and partitioned between heptane and 1 M aqueous hydrochloric acid. The organic layer was washed with 1 M aqueous hydrochloric acid and with water, then dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting solid was dissolved in methanol (30 mL), treated with decolorizing carbon, stirred for 10 minutes, and filtered through diatomaceous earth. Removal of solvent under reduced pressure provided the product as an off-white solid. Yield: 510 mg, 1.77 mmol, 53%. GCMS m/z 288.1 [M\(^+\)]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.83 (d, \(J=7.8\) Hz, 1H), 7.27 (d, \(J=9.6\) Hz, 1H), 6.57 (t, \(J_{HF}=73.8\) Hz, 1H), 4.42 (q, \(J=7.2\) Hz, 2H), 2.77 (s, 3H), 1.45 (t, \(J=7.1\) Hz, 3H).

Step 6. Synthesis of 5-(difluoromethoxy)-4-fluoro-1a-methyl-1a-dihydro-6bH-cycloprop[a][1]benzofuran-6b-carboxylic acid (C56).

Potassium tert-butoxide (1.0 M solution, 2.1 mL, 2.1 mmol) was added to a suspension of trimethylsulfonium iodide (98%, 0.477 g, 2.12 mmol) in dimethyl sulfoxide (4.5 mL), and the mixture was allowed to stir at room temperature for 30 minutes. A solution of C55 (510 mg, 1.77
mmol) in tetrahydrofuran (2.5 mL) was then introduced in a drop-wise manner over 15 minutes, and the reaction mixture was stirred at room temperature for 1 hour. Crushed potassium hydroxide pellets (85%, 0.292 g, 4.42 mmol) were added, and stirring was continued for 1 hour, whereupon the reaction mixture was cooled in an ice bath, diluted with water (25 mL), and washed with heptane (50 mL). The aqueous layer was cooled in an ice bath and adjusted to a pH of 4 – 5 via addition of concentrated hydrochloric acid. The mixture was extracted with diethyl ether, and the combined organic layers were washed with water and with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. The product was obtained as a thick oil, which solidified to a yellow-orange solid upon standing. Yield: 214 mg, 0.780 mmol, 44%. LCMS m/z 273.4 [M–H⁻]. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J=7.9 Hz, 1H), 6.68 (d, J=10 Hz, 1H), 6.48 (t, J₆F=73.9 Hz, 1H), 2.04 (d, J=6.2 Hz, 1H), 1.88 (s, 3H), 0.99 (d, J=6.2 Hz, 1H).

Step 7. Synthesis of 5-(difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-carboxamide (C57).

Compound C56 (214 mg, 0.780 mmol) was converted to the product using the method described for synthesis of C38 from C37 in Examples 6 and 7. The product was obtained as a thick oil (200 mg) that contained significant solvent via ¹H NMR analysis; this material was taken directly to the following step. GCMS m/z 273.1 [M⁺]. ¹H NMR (400 MHz, CDCl₃), product peaks only: δ 7.33 (d, J=7.6 Hz, 1H), 6.73 (d, J=10.2 Hz, 1H), 6.49 (t, J₆F=73.5 Hz, 1H), 5.77-5.99 (br m, 2H), 2.11 (d, J=6.3 Hz, 1H), 1.74 (s, 3H), 0.77 (d, J=6.3Hz, 1H).

Step 8. Synthesis of 1-[5-(difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methanamine (C58).

A solution of C57 (from the previous step; 200 mg, <0.73 mmol) in toluene (2 mL) was cooled in an ice bath and slowly treated with sodium bis(2-methoxyethoxy)aluminum hydride (3.3 M solution in toluene, 0.56 mL, 1.8 mmol), while the internal reaction temperature was kept below 15 ºC. Upon completion of the addition, the ice bath was removed and the reaction mixture was allowed to warm to room temperature and stir overnight. Sodium bis(2-methoxyethoxy)aluminum hydride (3.3 M solution in toluene, 2.2 mL, 7.3 mmol) was again added, and stirring was continued at room temperature for 24 hours, whereupon additional sodium bis(2-methoxyethoxy)aluminum hydride (3.3 M solution in toluene, 2.7 mL, 8.9 mmol) was introduced. After the reaction mixture had stirred at room temperature for 24 hours, it was heated at 50 ºC for 24 hours. It was then allowed to cool to room temperature, further cooled in an ice bath, and quenched via slow addition
of aqueous sodium hydroxide solution (1 M, 50 mL), while the internal temperature was maintained below 30 °C. This mixture was stirred for 15 minutes, whereupon it was extracted with diethyl ether (3 x 20 mL); the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford the product as a thick oil (105 mg), which was substantially impure via ¹H NMR analysis. This material was used directly in the following step. GCMS m/z 242.1 [M–NH₂⁺].

Step 9. Synthesis of 2-[[1aS,6bS]-5-(difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (12) and 2-[[1aR,6bR]-5-(difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (13).

1,3,4,6,7,8-Hexahydro-2H-pyrimido[1,2-a]pyrimidine (97%, 94.7 mg, 0.660 mmol) was added to a mixture of C58 (from the previous step; 105 mg, <0.40 mmol) and C10 (129 mg, 0.526 mmol) in N,N-dimethylformamide (1 mL), and the reaction mixture was stirred at room temperature for 2 hours. Ethyl trifluoroacetate (0.12 mL, 1.01 mmol) was added, and after an additional hour of stirring, the reaction mixture was treated with aqueous sodium hydroxide solution (1 M, 1.5 mL) and allowed to stir for 30 minutes, whereupon it was extracted three times with ethyl acetate. The combined organic layers were washed twice with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was subjected to chromatography on silica gel (Gradient: 0% to 3% methanol in dichloromethane), followed by purification using supercritical fluid chromatography [Column: Chiral Technologies Chiralpak AD-H, 5 μm; Mobile phase: 30% (methanol containing 0.6% ammonium hydroxide) in carbon dioxide].

Compound 12 was the second-eluting enantiomer. Yield: 4.4 mg, 9.0 μmol, 1.2% over three steps. LCMS m/z 487.3 [M+H⁺]. Retention time: 3.86 minutes (Analysis via supercritical fluid chromatography [Column: Chiral Technologies Chiralpak AD-H, 4.6 x 100 mm, 5 μm; Mobile phase: 40% (methanol containing 0.6% ammonium hydroxide) in carbon dioxide; Flow rate: 1.5 mL/minute]).

The first-eluting enantiomer was 13. Yield: 4.4 mg, 9.0 μmol, 1.2% over three steps. LCMS m/z 487.3 [M+H⁺]. Retention time: 2.81 minutes using an analytical system identical to that employed for 12.
Example 14
2-[[((1αS,6bS)-4-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl]-7-[4-(hydroxymethyl)-1H-imidazol-1-yl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (14)

Compound 6 (0.4 mg, 800 nmol) was incubated with liver microsomes (from male monkeys; 1.5 mg/mL), magnesium chloride (3.3 mM), and NADPH (1.3 mM), in 0.1 M potassium phosphate buffer (pH 7.4; total volume of incubation solution, 40 mL). The reaction mixture was shaken at 37°C in a water bath for 67 minutes, whereupon acetonitrile (40 mL) was added and the mixture was spun at 1700g for 5 minutes. The supernatant was subjected to vacuum centrifugation to a volume of approximately 15 mL, to which was added formic acid (0.5 mL), acetonitrile (0.5 mL), and water (sufficient to reach a total volume of 50 mL). This mixture was spun at 40000g for 30 minutes. The supernatant was purified via reversed phase chromatography (Column: Agilent Polaris C18, 5 μm; Mobile phase A: 0.1% aqueous formic acid; Mobile phase B: acetonitrile; Gradient: 1% to 90% B) to afford the product. Yield: 17 μg, 32 nmol, 4%. LCMS m/z 521.1 [M+H]⁺. 1H NMR (600 MHz, DMSO-d₆), characteristic peaks: 8 8.25 (s, 1H), 7.84 (d, J=7.8 Hz, 1H), 7.52 (s, 1H), 7.49 (d, J=7.8 Hz, 1H), 7.07-7.12 (m, 2H), 4.58 (d, J=15.0 Hz, 1H), 4.39 (s, 2H), 4.16-4.22 (m, 1H), 4.13 (ddd, half of ABXY pattern, J=14, 8, 4 Hz, 1H), 3.68-3.74 (m, 1H), 3.54 (d, J=15.1 Hz, 1H), 3.50 (ddd, J=13, 8, 4 Hz, 1H), 1.80 (s, 3H), 0.59 (d, J=6.4 Hz, 1H).

<table>
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<tr>
<th>Example Number</th>
<th>Method of Preparation; Non-commercial starting materials</th>
<th>Structure</th>
<th>(^1)H NMR (400 MHz, CDCl(_3), (\delta); LCMS, observed ion m/z [M+H]+</th>
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<tr>
<td>15</td>
<td>Examples 4 and 5(^1)</td>
<td><img src="image" alt="Structure Image" /></td>
<td>8.19-8.25 (m, 1H), 7.56-7.59 (m, 1H), 7.45 (d, (J=7.6) Hz, 1H), 7.40 (br d, (J=8.4) Hz, 1H), 7.30 (d, (J=7.8) Hz, 1H), 7.09-7.15 (m, 1H), 6.90 (d, (J=8.3) Hz, 1H), 5.04 (d, (J=15.2) Hz, 1H), 4.25-4.33 (m, 1H), 4.20 (ddd, half of ABXY pattern, (J=14, 8, 4) Hz, 1H), 3.58 (ddd, half of ABXY pattern, (J=13, 6, 4) Hz, 1H), 3.46 (ddd, half of ABXY pattern, (J=13, 8, 4) Hz, 1H), 3.27 (d, (J=15.1) Hz, 1H), 2.28 (br s, 3H), 1.86 (s, 3H), 1.04 (d, (J=6.5) Hz, 1H), 0.67 (d, (J=6.5) Hz, 1H); 471.0</td>
</tr>
<tr>
<td>16</td>
<td>Examples 4 and 5(^1)</td>
<td><img src="image" alt="Structure Image" /></td>
<td>8.19-8.23 (m, 1H), 7.56-7.59 (m, 1H), 7.45 (d, (J=7.8) Hz, 1H), 7.40 (br d, (J=6.3) Hz, 1H), 7.30 (d, (J=7.6) Hz, 1H), 7.10-7.14 (m, 1H), 6.90 (d, (J=8.3) Hz, 1H), 5.04 (d, (J=15.3) Hz, 1H), 4.25-4.33 (m, 1H), 4.20 (ddd, half of ABXY pattern, (J=14, 8.5, 4) Hz, 1H), 3.54-3.62 (m, 1H), 3.46 (ddd, half of ABXY pattern, (J=13, 8.5, 4) Hz, 1H), 3.27 (d, (J=15.2) Hz, 1H), 2.28 (s, 3H), 1.86 (s, 3H), 1.04 (d, (J=6.6) Hz, 1H), 0.67 (d, (J=6.5) Hz, 1H); 471.0</td>
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<tr>
<td>17</td>
<td>Examples 2 and 3&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>^H NMR (400 MHz, CD&lt;sub&gt;3&lt;/sub&gt;OD), δ 8.42-8.49 (br s, 1H), 7.81 (d, J=7.7 Hz, 1H), 7.67 (br d, J=7.4 Hz, 1H), 7.34-7.39 (br s, 1H), 7.28 (d, J=7.8 Hz, 1H), 6.79 (br d, J=11 Hz, 1H), 4.81-4.90 (m, 1H, assumed; partially obscured by water peak), 4.29-4.37 (m, 1H), 4.20 (ddd, half of ABXY pattern, J=14, 9, 4 Hz, 1H), 3.69-3.78 (m, 1H), 3.50-3.59 (m, 1H), 3.50 (d, J=15.2 Hz, 1H), 2.26 (s, 3H), 1.87 (s, 3H), 1.20 (d, J=6.6 Hz, 1H), 0.62 (d, J=6.6 Hz, 1H); 489.4</td>
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<td>18</td>
<td>Examples 2 and 3&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>^H NMR (400 MHz, CD&lt;sub&gt;3&lt;/sub&gt;OD), δ 8.28 (br s, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.67 (br d, J=7.3 Hz, 1H), 7.28-7.31 (br s, 1H), 7.27 (d, J=7.7 Hz, 1H), 6.79 (br d, J=11.2 Hz, 1H), 4.82-4.87 (m, 1H, assumed; partially obscured by water peak), 4.33 (ddd, half of ABXY pattern, J=14.2, 6.2, 4.3 Hz, 1H), 4.20 (ddd, half of ABXY pattern, J=14.2, 8.7, 4.2 Hz, 1H), 3.73 (ddd, J=13.2, 6.2, 4.3 Hz, 1H), 3.54 (ddd, J=13.3, 8.7, 4.2 Hz, 1H), 3.50 (d, J=15.2 Hz, 1H), 2.23 (d, J=0.8 Hz, 3H), 1.87 (s, 3H), 1.20 (d, J=6.6 Hz, 1H), 0.62 (d, J=6.7 Hz, 1H); 489.4</td>
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19  Examples 4 and 5\textsuperscript{a}  

8.20 (br s, 1H), 7.44 (d, J=7.8 Hz, 1H), 7.40-7.42 (m, 1H), 7.28 (d, J=7.6 Hz, 1H), 7.20 (br d, J=10.3 Hz, 1H), 7.11 (br s, 1H), 5.03 (d, J=15.2 Hz, 1H), 4.34 (ddd, half of ABXY pattern, J=14.3, 6.3, 4.3 Hz, 1H), 4.18 (ddd, half of ABXY pattern, J=14.3, 8.7, 4.3 Hz, 1H), 3.58 (ddd, half of ABXY pattern, J=13.0, 6.2, 4.3 Hz, 1H), 3.48 (ddd, half of ABXY pattern, J=13.1, 8.6, 4.1 Hz, 1H), 3.24 (d, J=15.2 Hz, 1H), 2.27 (br s, 3H), 1.90 (s, 3H), 1.11 (d, J=6.9 Hz, 1H), 0.75 (d, J=6.8 Hz, 1H); 489.2

20  Examples 4 and 5\textsuperscript{a}  

8.21 (br s, 1H), 7.44 (d, J=7.8 Hz, 1H), 7.40-7.43 (m, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.21 (br d, J=10.4 Hz, 1H), 7.11 (br s, 1H), 5.04 (d, J=15.2 Hz, 1H), 4.35 (ddd, half of ABXY pattern, J=14, 6, 4 Hz, 1H), 4.19 (ddd, half of ABXY pattern, J=14, 8.5, 4 Hz, 1H), 3.58 (ddd, half of ABXY pattern, J=13, 6, 4 Hz, 1H), 3.48 (ddd, half of ABXY pattern, J=13, 8.5, 4 Hz, 1H), 3.25 (d, J=15.3 Hz, 1H), 2.28 (s, 3H), 1.90 (s, 3H), 1.11 (d, J=6.9 Hz, 1H), 0.75 (d, J=6.9 Hz, 1H); 489.2

21  Examples 4 and 5\textsuperscript{a, b}  

8.20-8.23 (m, 1H), 7.50-7.53 (m, 1H), 7.44 (d, J=7.6 Hz, 1H), 7.42-7.45 (m, 1H), 7.28 (d, J=7.6 Hz, 1H), 7.10-7.13 (m, 1H), 5.07 (d, J=15.2 Hz, 1H), 4.37 (ddd, half of ABXY pattern, J=14, 6, 4 Hz, 1H), 4.18 (ddd, half of ABXY pattern, J=14, 9, 4 Hz, 1H), 3.53-3.61 (m, 1H), 3.48 (ddd, half of ABXY pattern, J=13, 9, 4 Hz, 1H), 3.22 (d, J=15.3 Hz, 1H), 2.28 (br s, 3H), 1.92 (s, 3H), 1.11 (d, J=6.8 Hz, 1H), 0.75 (br d, J=6.7 Hz, 1H); 505.0
<table>
<thead>
<tr>
<th>22</th>
<th>Examples 4 and 5(^5,6)</th>
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</table>

| 8.21 (d, \(J=1.1\ Hz, 1\)H), 7.50-7.53 (m, 1H), 7.44 (d, \(J=7.8\ Hz, 1\)H), 7.42-7.44 (m, 1H), 7.28 (d, \(J=7.9\ Hz, 1\)H), 7.10-7.13 (m, 1H), 5.07 (d, \(J=15.2\ Hz, 1\)H), 4.37 (ddd, half of ABXY pattern, \(J=14.3, 6.0, 4.2\ Hz, 1\)H), 4.18 (ddd, half of ABXY pattern, \(J=14.4, 8.8, 4.2\ Hz, 1\)H), 3.57 (ddd, half of ABXY pattern, \(J=13.0, 6.2, 4.2\ Hz, 1\)H), 3.48 (ddd, half of ABXY pattern, \(J=13.0, 8.7, 4.1\ Hz, 1\)H), 3.22 (d, \(J=15.2\ Hz, 1\)H), 2.28 (d, \(J=0.8\ Hz, 3\)H), 1.92 (s, 3H), 1.11 (d, \(J=6.8\ Hz, 1\)H), 0.75 (d, \(J=6.9\ Hz, 1\)H); 505.0 |

1. Examples 15 and 16 were isolated from the racemic mixture via supercritical fluid chromatography (Column: Chiral Technologies Chiralpak AD-3, 3 \(\mu\)m; Mobile phase A: carbon dioxide; Mobile phase B: methanol containing 0.05% diethylamine; Gradient: 5% to 40% B). Analytical supercritical fluid chromatography (Column: Chiralpak AD-3, 150 x 4.6 mm, 3 \(\mu\)m; Mobile phase A: carbon dioxide; Mobile phase B: methanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 5.5 min, then 40% B for 2 minutes; Flow rate: 2.5 mL/minute) yielded a retention time of 5.69 minutes for Example 15, and a retention time of 5.42 minutes for Example 16.

2. The requisite 5-fluoro-2-iodo-4-(trifluoromethyl)phenol was synthesized via treatment of a solution of 3-fluoro-4-(trifluoromethyl)phenol in acetic acid with N-iodosuccinimide and sulfuric acid.

3. Examples 17 and 18 were isolated from the racemic mixture via supercritical fluid chromatography [Column: Princeton PPU, 5 \(\mu\)m; Mobile phase: 30% (0.2% ammonium hydroxide in ethanol) in carbon dioxide]. Example 17 was the second-eluting enantiomer in this system, with Example 18 eluting first.

4. Examples 19 and 20 were isolated from the racemic mixture via supercritical fluid chromatography [Column: Chiral Technologies Chiralpak AD, 10 \(\mu\)m; Mobile phase: 35% (methanol containing 0.1% ammonium hydroxide) in carbon dioxide]. Example 19 was the second-eluting enantiomer in this system, with Example 20 eluting first.

5. In this case, cleavage of the benzyl ether was not carried out via hydrogenation; instead, treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dichloromethane afforded the corresponding aldehyde, which was reduced using sodium borohydride.

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6. Examples 21 and 22 were isolated from the racemic mixture via supercritical fluid chromatography [Column: Chiral Technologies Chiralpak AD, 5 μm, Mobile phase: 40% (methanol containing 0.05% diethylamine) in carbon dioxide]. Example 21 was the second-eluting enantiomer in this system, with Example 22 eluting first.

Cell-based γ-secretase assay with ELISA readout

The ability of compounds to modulate production of amyloid beta protein Aβ(1-42) was determined using human WT-APP overexpressing CHO cells. Cells were plated at 22,000 cells/100 μL well in 96 well tissue culture treated, clear plates (Falcon) in DMEM/F12 based medium and incubated for 24 h at 37 °C. Compounds for testing were diluted in 100% DMSO to achieve an eleven point, half log, dose response for IC50 determinations. Compounds were added in fresh medium to achieve 1% final DMSO. Appropriate vehicle or inhibitor controls were added into control wells individually to obtain minimum or maximum inhibition values, respectively, for the assay signal window before the plates were incubated for ~24 h at 37 °C. This procedure produces conditioned media in each well, which is tested for Aβ(1-42) levels in the ELISA detection step described next. The remaining cell cultures in each well are also tested for cell toxicity as described below.

Coating of ELISA assay plates was initiated by addition of 50 μL/well of an in-house Aβ(1-42) specific antibody (3 μg/mL) in 0.1 M NaHCO3 (pH 9.0) into black 384-well Maxisorp® plates (Nunc); incubation was carried out overnight at 4 °C. The capture antibody was then aspirated from the ELISA assay plates and plates were washed either 2 x 100 μL with a Matrical Squirt plate washer, or 3 x 90 μL with a Thermo Combi, using Wash Buffer (Dulbecco’s PBS, 0.05% Tween 20). 90 μL/well of Blocking Buffer (Dulbecco’s PBS, 1.0% BSA (Sigma A7030) was then added to plates. Ambient temperature incubation was allowed to proceed for a minimum of 2 h. Blocking Buffer was then removed and 20 μL/well Assay Buffer (Dulbecco’s PBS, 1.0% BSA (Sigma A7030), 0.05% Tween 20) was then added. At this point, 35 μL (40 μL prior to August, 2012) (in duplicate) of experimental conditioned media (described above) was transferred into wells of the blocked ELISA plates containing the capture antibody, followed by overnight incubation at 4 °C. Cell toxicity was also measured in the corresponding remaining cells after removal of the conditioned media for the Aβ(1-42) assay by a colorimetric cell proliferation assay (CellTiter 96® AQueous One Solution Cell Proliferation Assay, Promega) according to the manufacturer’s instructions.
After overnight incubation of the ELISA assay plates at 4 °C, unbound Aβ peptides were removed via either 2 x 100 µL washes with a Matrical Squirt plate washer, or 3 x 90 µL washes with a Thermo Combi, using Wash Buffer. Europium (Eu) labeled (custom labeled, PerkinElmer) Aβ(1-16) 6e10 Monoclonal Antibody (Covance #SIG-39320) was added, (50 µL/well Eu-6e10 @ 1:10,000, 20 uM EDTA) in Assay Buffer. Incubation at ambient temperature for a minimum of 2 h was followed by either 2 x 100 µL washes with a Matrical Squirt plate washer, or 3 x 90 µL washes with a Thermo Combi, using Wash Buffer, before 30 µL/well of Delfia Enhancement Solution (PerkinElmer) was added. Following 30 to 60 min ambient temperature incubation, the plates were read on an EnVision plate reader (PerkinElmer) using standard DELFIA TRF settings. Data analysis including inhibitory IC_{50} determination was performed using nonlinear regression fit analysis (in-house software) and the appropriate plate mean values for the maximum and minimum inhibition controls.

Biological data for the compounds of Examples 1-22 and C22, C33, C40 and C44 are found in Table 7 below:

<table>
<thead>
<tr>
<th>Example Number</th>
<th>Aβ 42B IC_{50} (nM)</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48.5</td>
<td>7-(4-methyl-1H-imidazol-1-yl)-2-[[5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</td>
</tr>
<tr>
<td>C22</td>
<td>19.5</td>
<td>7-(4-methyl-1H-imidazol-1-yl)-2-[[1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</td>
</tr>
<tr>
<td>2</td>
<td>6.5</td>
<td>7-(4-methyl-1H-imidazol-1-yl)-2-[[1aS,6bS]-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</td>
</tr>
<tr>
<td>3</td>
<td>59.2</td>
<td>7-(4-methyl-1H-imidazol-1-yl)-2-[[1aR,6bR]-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</td>
</tr>
<tr>
<td>C33</td>
<td>9.3a</td>
<td></td>
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<tr>
<td>-----</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>C40</td>
<td>11.2</td>
<td></td>
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<tr>
<td>C44</td>
<td>68.9</td>
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<tr>
<td>4</td>
<td>4.9</td>
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<tr>
<td>5</td>
<td>59.2</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
<td>38.0</td>
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<tr>
<td>8</td>
<td>36.6</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>519</td>
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</table>

2-[[3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6H-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-[[1aS,6bS]-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-[[1aR,6bR]-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-[[1aR,6bS]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-[[1aS,6bS]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-[[1aR,6bR]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-[[1aS,6bS]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-[[1aR,6bR]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-[[1aR,6bR]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

-100-
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
</table>
| 10 | 3.0<sup>b</sup> | 2-(((1S,6bS)-4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-
dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-
methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione |
| 11 | 10.0 | 2-(((1aR,6bR)-4-chloro-1a-methyl-5-(trifluoromethyl)-1a-
dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-
methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione |
| 12 | 17.8 | 2-(((1S,6bS)-5-(difluoromethoxy)-4-fluoro-1a-methyl-
1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-
methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione |
| 13 | 84.9 | 2-(((1aR,6bR)-5-(difluoromethoxy)-4-fluoro-1a-methyl-
1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-
methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione |
| 14 | 18.7 | 2-(((1S,6bS)-4-fluoro-1a-methyl-5-(trifluoromethoxy)-
1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-[4-
(hydroxymethyl)-1H-imidazol-1-yl]-3,4-dihydro-2H-pyrido[1,2-
a]pyrazine-1,6-dione |
| 15 | 8.5<sup>b</sup> | 7-(4-methyl-1H-imidazol-1-yl)-2-(((1S,6bS)-1a-methyl-5-
(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-
yl)methyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione |
| 16 | 47.3 | 7-(4-methyl-1H-imidazol-1-yl)-2-(((1aR,6bR)-1a-methyl-5-
(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-
yl)methyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione |
| 17 | 4.4<sup>b</sup> | 2-(((1S,6bS)-4-fluoro-1a-methyl-5-(trifluoromethyl)-1a-
dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-
methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione |
| 18 | 20.2 | 2-(((1aR,6bR)-4-fluoro-1a-methyl-5-(trifluoromethyl)-1a-
dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-
methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione |
<table>
<thead>
<tr>
<th></th>
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<th>2-(((1aS,6bS)-3-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>11.1</td>
<td>2-(((1aR,6bR)-3-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</td>
</tr>
<tr>
<td>20</td>
<td>50.1</td>
<td>2-(((1aS,6bS)-3-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</td>
</tr>
<tr>
<td>21</td>
<td>16.0</td>
<td>2-(((1aR,6bR)-3-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</td>
</tr>
<tr>
<td>22</td>
<td>58.3</td>
<td>2-(((1aR,6bR)-3-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione</td>
</tr>
</tbody>
</table>

a. Reported IC₅₀ value is from a single determination.
b. Reported IC₅₀ value is the geometric mean of ≥5 determinations.
We claim:

1. A compound having the structure of Formula I:

   ![Formula I](image)

   or pharmaceutically acceptable salts thereof, wherein:

   X is a (5- to 14-membered) heteroaryl containing 1-3 heteroatoms;

   $R^1$, where chemically permissible, is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₅-C₈)cycloalkyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R¹)(R²), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴;

   $R^{2a}$ and $R^{2b}$, where chemically permissible, at each occurrence, are independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₁-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or $R^{2a}$ and $R^{2b}$ together with the carbon atom(s) to which they are attached form a (C₅-C₈)cycloalkyl or a (4- to 10-membered) heterocycloalkyl, wherein the (C₅-C₈)cycloalkyl and the (4- to 10-membered) heterocycloalkyl are optionally substituted with one to three $R^8$;

   $R^{4a}$ and $R^{4b}$, where chemically permissible, are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, and pharmaceutically acceptable salts thereof.
substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or R⁵⁻ and R⁶⁻ together with the carbon atom to which they are attached form a (C₃-C₆)cycloalkyl, wherein the (C₃-C₆)cycloalkyl is optionally substituted with one to three R⁵⁻.

R⁵⁻ and R⁶⁻, at each occurrence, are independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or R⁵⁻ and R⁶⁻ together with the carbon atom to which they are attached form a (C₃-C₆)cycloalkyl, wherein said (C₃-C₆)cycloalkyl is optionally substituted with one to three R⁶⁻.

R⁵ and R⁷ are each independently selected from the group consisting of hydrogen, halogen, cyano, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl, optionally substituted (C₃-C₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, -C(=O)-OR⁴, and -OR⁴, provided that R⁵⁻ and R⁷ cannot both be hydroxy;

R⁶⁻, at each occurrence, is independently selected from the group consisting of cyano, halogen, hydroxy, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, and optionally substituted (C₁-C₆)alkoxy(C₁-C₆)alkyl;

R⁶⁻ is selected from the group consisting of hydrogen and optionally substituted (C₁-C₆)alkyl;
y is an integer selected from 1, 2, 3 or 4;

ring B is optionally substituted with one to three R¹⁰⁻, wherein each R¹⁰⁻ is independently selected from the group consisting of halogen, cyano, hydroxy, -SF₅, nitro, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted thio(C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, optionally substituted (C₃-C₆)cycloalkyl, -N(R⁴)(R⁵), -N(R⁴)(C=O)R⁵, -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)-R⁴, and -C(=O)-OR⁴; or two R¹⁰⁻ substituents taken together with the carbon atom(s) to which they are attached form an optionally substituted (C₃-C₆)cycloalkyl;
ring D is optionally substituted with one to four \( R^{11} \), wherein each \( R^{11} \) is independently selected from the group consisting of halogen, cyano, hydroxy, -SF\(_5\), nitro, optionally substituted (\( C_1-C_6 \)alkyl, optionally substituted (\( C_2-C_6 \)alkenyl, optionally substituted (\( C_2-C_6 \)alkynyl, optionally substituted thio(\( C_1-C_6 \)alkyl, optionally substituted (\( C_1-C_6 \)alkoxy, optionally substituted (\( C_3-C_8 \)cycloalkyl, optionally substituted \((4-\) to \(6-\)membered)heterocycloalkyl; \(-N(R^4)(R^5), -N(R^4)(C(O)R^5), -C(=O)N(R^4)(R^5), -O-C(=O)N(R^4)(R^5), -C(=O)-R^4, -C(=O)-OR^4\); and

\( R^4 \) and \( R^5 \), at each occurrence, are each independently selected from hydrogen or optionally substituted (\( C_1-C_6 \)alkyl);

provided that the compound is not \( 7-(4\)-methyl-1\( H\)-imidazol-1-\( yl)\)-2-\{[5-(trifluoromethyl)-1,1a-dihydro-6b\( H\)cyclopropa[b][1]benzofuran-6b-\( yl\)methyl]-3,4-dihydro-2\( H\)-pyrido[1,2-a]pyrazine-1,6-dione.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

\( X \) is represented by:

(i) a (5- to 6-membered)heteroaryl containing 1-3 heteroatoms;

(ii) a (6-membered)heteroaryl containing 1-3 heteroatoms; or

(iii) a (5-membered)heteroaryl containing 1-3 heteroatoms.

3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein

\( X \) is a (5-membered)heteroaryl selected from the group consisting of triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, isothiazolyl, thiazolyl, isoxazolyl, and oxazolyl.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein

\( X \) is imidazolyl.

5. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein

\( X \) is triazolyl.

6. The compound according to any one of claims 2 to 5, or a pharmaceutically acceptable salt thereof, wherein:

\( R^1 \), where chemically permissible, is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF\(_5\), nitro, optionally substituted (\( C_1-C_6 \)alkyl, optionally substituted
(C₂₋₆)alkenyl, optionally substituted (C₂₋₆)alkynyl, optionally substituted thio(C₁₋₆)alkyl, optionally substituted (C₁₋₆)alkoxy, optionally substituted (C₃₋₆)cycloalkyl, -N(R¹)(R²), -N(R³)(C(=O)R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)R⁴, and -C(=O)-OR⁵;

R²ᵃ and R²ᵇ, where chemically permissible, at each occurrence, are independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, -SF₅, nitro, optionally substituted (C₁₋₆)alkyl, optionally substituted (C₂₋₆)alkenyl, optionally substituted (C₂₋₆)alkynyl, optionally substituted thio(C₁₋₆)alkyl, optionally substituted (C₁₋₆)alkoxy, optionally substituted (C₁₋₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C(=O)R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)R⁴, and -C(=O)-OR⁵; or R²ᵃ and R²ᵇ together with the carbon atom(s) to which they are attached form a (C₃₋₆)cycloalkyl or a (4- to 10-membered) heterocycloalkyl, wherein the (C₃₋₆)cycloalkyl and the (4- to 10-membered) heterocycloalkyl are optionally substituted with one to three R⁸;

R⁴ᵃ and R⁴ᵇ, where chemically permissible, are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁₋₆)alkyl, optionally substituted (C₂₋₆)alkenyl, optionally substituted (C₂₋₆)alkynyl, optionally substituted thio(C₁₋₆)alkyl, optionally substituted (C₁₋₆)alkoxy, optionally substituted (C₁₋₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C(=O)R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)R⁴, and -C(=O)-OR⁵; or R⁴ᵃ and R⁴ᵇ together with the carbon atom to which they are attached form a (C₃₋₆)cycloalkyl, wherein the (C₃₋₆)cycloalkyl is optionally substituted with one to three R⁸;

R⁶ᵃ and R⁶ᵇ, at each occurrence, are independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF₅, nitro, optionally substituted (C₁₋₆)alkyl, optionally substituted (C₂₋₆)alkenyl, optionally substituted (C₂₋₆)alkynyl, optionally substituted thio(C₁₋₆)alkyl, optionally substituted (C₁₋₆)alkoxy, optionally substituted (C₁₋₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C(=O)R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -C(=O)R⁴, and -C(=O)-OR⁵; or R⁶ᵃ and R⁶ᵇ together with the carbon atom to which they are attached form a (C₃₋₆)cycloalkyl, wherein said (C₃₋₆)cycloalkyl is optionally substituted with one to three R⁸;

R⁸ and R⁷ are each independently selected from the group consisting of hydrogen, halogen, cyano, -SF₅, nitro, optionally substituted (C₁₋₆)alkyl, optionally substituted (C₂₋₆)alkenyl, optionally substituted (C₂₋₆)alkynyl, optionally substituted thio(C₁₋₆)alkyl, optionally substituted (C₁₋₆)alkoxy, optionally substituted (C₁₋₆)cycloalkyl, optionally substituted phenyl, -N(R⁴)(R⁵), -N(R⁴)(C(=O)R⁵), -C(=O)N(R⁴)(R⁵), -O-C(=O)N(R⁴)(R⁵), -O-
C(=O)N(R^4)(R^5), -C(=O)-R^4, -C(=O)-OR^4, and -OR^5; provided that R^6 and R^7 cannot both be hydroxy;

R^8, at each occurrence, is independently selected from the group consisting of cyano, halogen, hydroxy, -SF_5, nitro, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, and optionally substituted (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R^9 is selected from the group consisting of hydrogen and optionally substituted (C_1-C_6)alkyl; y is an integer selected from 1, 2, 3 or 4;

ring B is optionally substituted with one to three R^{10}, wherein each R^{10} is independently selected from the group consisting of halogen, cyano, hydroxy, -SF_5, nitro, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl, optionally substituted (C_2-C_6)alkynyl, optionally substituted thio(C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_3-C_8)cycloalkyl, -N(R^4)(R^5), -N(R^4)(C(=O)R^5), -C(=O)N(R^4)(R^5), -O-C(=O)N(R^4)(R^5), -C(=O)R^4, -C(=O)-OR^4; or two R^{10} substituents taken together with the carbon atom(s) to which they are attached form an optionally substituted (C_2-C_6)cycloalkyl;

ring D is optionally substituted with one to four R^{11}, wherein each R^{11} is independently selected from the group consisting of halogen, cyano, hydroxy, -SF_5, nitro, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl, optionally substituted (C_2-C_6)alkynyl, optionally substituted thio(C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted (4- to 6-membered)heterocycloalkyl; -N(R^4)(R^5), -N(R^4)(C(=O)R^5), -C(=O)N(R^4)(R^5), -O-C(=O)N(R^4)(R^5), -C(=O)-R^4, -C(=O)-OR^4; and

R^4 and R^5, at each occurrence, are each independently selected from hydrogen or optionally substituted (C_1-C_6)alkyl.

7. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, optionally substituted (C_1-C_6)alkyl, and optionally substituted (C_1-C_6)alkoxy; wherein the (C_1-C_6)alkyl and (C_1-C_6)alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF_5;

R^{2a} and R^{2b} are each independently selected from hydrogen, halogen, cyano, hydroxy or optionally substituted (C_1-C_6)alkyl;

R^{4a}, R^{4b}, R^{5a} and R^{5b} are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxy, oxo, -SF_5, optionally substituted (C_1-C_6)alkyl, and optionally
substituted (C₁-C₆)alkoxy, wherein the (C₁-C₆)alkyl and (C₁-C₆)alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF₅;

R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, cyano, halogen, -SF₅, optionally substituted (C₁-C₆)alkyl, and optionally substituted (C₁-C₆)alkoxy, wherein the (C₁-C₆)alkyl and (C₁-C₆)alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF₅;

y is 1;

ring B is optionally substituted with one to two R¹⁰, wherein each R¹⁰ is independently selected from halogen, cyano, hydroxy, -SF₅, optionally substituted (C₁-C₆)alkyl, and optionally substituted (C₁-C₆)alkoxy, wherein the (C₁-C₆)alkyl and (C₁-C₆)alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF₅; and

ing D is optionally substituted with one to three R¹¹, wherein each R¹¹ is independently selected from the group consisting of halogen, cyano, hydroxy, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₁-C₆)alkoxy, -SF₅, -N(R⁴)(R⁵), nitro, and optionally substituted (C₃-C₈)cycloalkyl, wherein the (C₁-C₆)alkyl, (C₁-C₆)alkoxy, and (C₃-C₈)cycloalkyl are optionally substituted with one to three substituents independently selected from halogen, cyano, hydroxy, -SF₅, and optionally substituted (C₁-C₆)alkyl, wherein R⁴ and R⁵ are each independently selected from hydrogen or optionally substituted (C₁-C₆)alkyl.

8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein:

R¹ is an optionally substituted (C₁-C₆)alkyl, wherein the (C₁-C₆)alkyl is substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF₅; and

R²a, R²b, R⁴a, R⁴b, R⁵a and R⁵b are each independently

i) hydrogen; or

ii) optionally substituted (C₁-C₆)alkyl, wherein the (C₁-C₆)alkyl is substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF₅.

9. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein

R¹ is methyl; and R²a, R²b, R⁴a, R⁴b, R⁵a and R⁵b are each independently hydrogen.
10. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein R¹ is methyl; R²a, R²b, R⁵a and R⁵b are each independently hydrogen; and one of R⁴a and R⁴b is hydrogen and the other is methyl.

11. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein R¹ is methyl; one of R²a and R²b is hydrogen and the other is methyl; R⁴a, R⁴b, R⁵a and R⁵b are each independently hydrogen.

12. A compound having the structure of Formula II:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, optionally substituted (C₁-C₆)alkyl, and optionally substituted (C₁-C₆)alkoxy; wherein the (C₁-C₆)alkyl and (C₁-

15 C₆)alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF₆;

R²a, R²b, R⁴a, R⁴b, R⁵a and R⁵b are each independently selected from hydrogen, halogen, cyano, hydroxy or optionally substituted (C₁-C₆)alkyl;

ring B is optionally substituted with one to two R¹⁰, wherein each R¹⁰ is independently selected from halogen or optionally substituted (C₁-C₆)alkyl; and

ring D is optionally substituted with one to three R¹¹, wherein each R¹¹ is independently selected from halogen, optionally substituted (C₁-C₆)alkyl, and optionally substituted (C₁-C₆)alkoxy;
provided that the compound is not 7-(4-methyl-1H-imidazol-1-yl)-2-[[5-(trifluoromethyl)-1,1a-
dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl]methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-
dione.

13. The compound according to claim 12, wherein:

R¹ is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, (C₁-C₆)alkyl, and (C₁-C₆)alkoxy; wherein the (C₁-C₆)alkyl and (C₁-C₆)alkoxy are optionally substituted with one to three fluoro atoms;

R²ᵃ, R²ᵇ, R⁴ᵃ, R⁴ᵇ, R⁵ᵃ and R⁵ᵇ are each independently selected from hydrogen or (C₁-
C₆)alkyl, wherein the (C₁-C₆)alkyl is methyl;

ring B is optionally substituted with one to two R¹⁰, wherein each R¹⁰ is selected from:

i) halogen selected from fluoro or chloro, or

ii) (C₁-C₆)alkyl, wherein the (C₁-C₆)alkyl is methyl; and

ring D is optionally substituted with one to three R¹¹, wherein each R¹¹ is selected from:

i) halogen selected from fluoro or chloro;

ii) optionally substituted (C₁-C₆)alkyl selected from the group consisting of fluoromethyl, difluoromethyl, and trifluoromethyl; and

iii) optionally substituted (C₁-C₆)alkoxy, wherein the optionally substituted (C₁-
C₆)alkoxy is selected from the group consisting of fluoromethoxy, difluoromethoxy, trifluoromethoxy.

14. The compound according to claim 12, wherein R¹ is a (C₁-C₆)alkyl wherein the alkyl is methyl.

15. A compound having the structure of Formula III:
or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, optionally substituted (C₁-C₆)alkyl, and optionally substituted (C₁-C₆)alkoxy; wherein the (C₁-C₆)alkyl and (C₁-C₆)alkoxy are optionally substituted with one to three substituents selected from halogen, oxo, cyano, hydroxy, or -SF₅;

R²a, R²b, R⁴a, R⁴b, R⁵a and R⁵b are each independently selected from hydrogen, halogen, cyano, hydroxy or optionally substituted (C₁-C₆)alkyl;

ring B is optionally substituted with one to two R¹⁰, wherein each R¹⁰ is independently selected from halogen or optionally substituted (C₁-C₆)alkyl; and

ring D is optionally substituted with one to three R¹¹, wherein each R¹¹ is independently selected from halogen, optionally substituted (C₁-C₆)alkyl, and optionally substituted (C₁-C₆)alkoxy.

16. The compound according to claim 15, wherein:

R¹ is selected from the group consisting of hydrogen, halogen, cyano, hydroxy, (C₁-C₆)alkyl, and (C₁-C₆)alkoxy; wherein the (C₁-C₆)alkyl and (C₁-C₆)alkoxy are optionally substituted with one to three fluoro atoms;

R²a, R²b, R⁴a, R⁴b, R⁵a and R⁵b are each independently selected from hydrogen or (C₁-C₆)alkyl, wherein the (C₁-C₆)alkyl is methyl;

ring B is optionally substituted with one to two R¹⁰, wherein each R¹⁰ is selected from:

i) halogen selected from fluoro or chloro, or

ii) (C₁-C₆)alkyl, wherein the (C₁-C₆)alkyl is methyl; and

ring D is optionally substituted with one to three R¹¹, wherein each R¹¹ is selected from:

i) halogen selected from fluoro or chloro;
ii) optionally substituted \((C_1-C_6)\)alkyl selected from the group consisting of fluoromethyl, difluoromethyl, and trifluoromethyl; and

iii) optionally substituted \((C_1-C_6)\)alkoxy, wherein the optionally substituted \((C_1-C_6)\)alkoxy is selected from the group consisting of fluoromethoxy, difluoromethoxy, and trifluoromethoxy.

17. A compound selected from the group consisting of:

- 7-(4-methyl-1H-imidazol-1-yl)-2-\{(1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

- 7-(4-methyl-1H-imidazol-1-yl)-2-\{[(1aS,6bS)-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

- 7-(4-methyl-1H-imidazol-1-yl)-2-\{[(1aR,6bR)-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

- 7-\{(1aS,6bS)-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

- 2-\{[(1aR,6bR)-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

- 2-\{[(1aR,6bR)-3-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

- 7-(4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

- 7-\{(1aS,6bS)-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

- 7-(4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl\}methyl\}-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aS,6bS]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aR,6bR]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aS,6bS]-4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aR,6bR]-4-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aS,6bS]-5-(difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aR,6bR]-5-(difluoromethoxy)-4-fluoro-1a-methyl-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aS,6bS]-4-fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-[4-(hydroxymethyl)-1H-imidazol-1-yl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
7-(4-methyl-1H-imidazol-1-yl)-2-[[1aS,6bS]-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
7-(4-methyl-1H-imidazol-1-yl)-2-[[1aR,6bR]-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aS,6bS]-4-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aR,6bR]-4-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-[[1aR,6bR]-4-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl][methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(((1S,6bS)-3-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-(((1aR,6bR)-3-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-(((1aS,6bS)-3-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;
2-(((1aR,6bR)-3-chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione; or the
pharmacologically acceptable salts thereof.

18. 2-(((1aS,6bS)-4-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione or a pharmacologically acceptable salt thereof.

19. 2-(((1aR,6bR)-4-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione or a pharmacologically acceptable salt thereof.

20. 2-(((1aS,6bS)-3-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione, or a pharmacologically acceptable salt thereof.

21. 2-(((1aR,6bR)-3-Fluoro-1a-methyl-5-(trifluoromethoxy)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione, or a pharmacologically acceptable salt thereof.

22. 2-(((1aS,6bS)-4-Chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-
cyclopropa[b][1]benzofuran-6b-yl[methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione, or a pharmacologically acceptable salt thereof.
23. 2-(((1R,6bR)-4-Chloro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b][1]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione, or a pharmaceutically acceptable salt thereof.

24. 2-(((1aS,6bS)-4-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione, or a pharmaceutically acceptable salt thereof.

25. 2-(((1aR,6bR)-4-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione, or a pharmaceutically acceptable salt thereof.

26. 2-(((1aS,6bS)-3-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione, or a pharmaceutically acceptable salt thereof.

27. 2-(((1aR,6bR)-3-fluoro-1a-methyl-5-(trifluoromethyl)-1,1a-dihydro-6bH-cyclopropa[b]benzofuran-6b-yl)methyl)-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione, or a pharmaceutically acceptable salt thereof.

28. Use of a compound as defined in any one of claims 1-27 or a pharmaceutically acceptable salt thereof, for reducing the production of amyloid beta (Aβ) protein Aβ 42B.

29. A pharmaceutical composition comprising a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.