VMAT2 INHIBITORS AND METHODS OF USE

BACKGROUND

Technical Field

This disclosure relates to, *inter alia*, certain compounds, compositions, and pharmaceutical compositions thereof, that modulate the activity of the transporter protein vesicular monoamine transporter-2 (VMAT2) and are directed to methods useful in the treatment of transporter protein vesicular monoamine transporter-2 mediated disorders, such as, neurological or psychiatric diseases or disorders, including but not limited to, hyperkinetic movement disorders (*e.g.*, tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, ataxia, chorea (such as, chorea associated with Huntington's disease), dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors). The disclosure further relates to synthetic methods and intermediates useful in the preparation of compounds.

Description of the Related Technology

Dysregulation of dopaminergic systems is integral to several central nervous system (CNS) disorders, including neurological and psychiatric diseases and disorders. These neurological and psychiatric diseases and disorders include hyperkinetic movement disorders, and conditions, such as, schizophrenia and mood disorders. The transporter protein vesicular monoamine transporter-2 (VMAT2) plays an important role in presynaptic dopamine release and regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release.

(±)-Tetrabenazine ((±)-TBZ), has been used as a drug for decades. (±)-TBZ is reported as a potent, reversible inhibitor of catecholamine uptake by VMAT2 (IC_{50} = 3.2 nM) (see, *e.g.*, Scherman *et al.*, Proc. Natl. Acad. Sci. USA, (1983) 80:584-8) and is currently used in the treatment of various hyperkinetic disorders. Inhibition of VMAT2 by (±)-TBZ results in depletion of brain monoamines *in vivo* (see, *e.g.*, Pettibone *et al.*, Eur. J. Pharmacol. (1984) 102:431-6). (±)-TBZ also inhibits presynaptic and postsynaptic dopamine receptors in rat brain (see, *e.g.*, Login *et al.*, (1982) Ann. Neurology 12:257-62; Reches *et al.*, J. Pharmacol. Exp. Ther. (1983) 225:515-521). (±)-TBZ exhibits extensive first pass metabolism following oral administration to humans with little or no (±)-TBZ observed in systemic circulation. The pharmacological activity of (±)-TBZ is therefore thought to be mediated primarily by active metabolites. (±)-TBZ has two chiral centers and is a racemic mixture of two stereoisomers. (±)-TBZ has been determined to be rapidly and extensively metabolized *in vivo* by carbonyl reductase to four metabolic stereoisomers of 3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-ol, also known as dihydrotetrabenazine (DHTBZ). The inhibitory constants of these four metabolites for VMAT2 have been reported, such as, in WO2008/058261, **EXAMPLE 7**. As shown, only two of the four DHTBZ isomers ([+]-alpha-DHTBZ and [+]-beta-DHTBZ) show significant potency as inhibitors of VMAT2.

(±)-TBZ Metabolite	pK_i	K_i
[+]-alpha-DHTBZ (2*R*,3*R*,11b*R*)	8.7 ± 0.2 (n=6)	1.9 nM
[+]-beta-DHTBZ (2*S*,3*R*,11b*R*)	7.9 ± 0.1 (n=5)	13 nM
[-]-alpha-DHTBZ (2*S*,3*S*,11b*S*)	6.7 ± 0.1 (n=3)	202 nM
[-]-beta-DHTBZ (2*R*,3*S*,11b*S*)	6.1 ± 0.1 (n=4)	714 nM

In patients administered (±)-TBZ, [-]-alpha-DHTBZ (2*S*,3*S*,11b*S*-DHTBZ) and [+]-beta-DHTBZ (2*S*,3*R*,11b*R*-DHTBZ) were the most abundant DHTBZ isomers, while [-]-beta-DHTBZ (2*R*,3*S*,11b*S*-DHTBZ) and [+]-alpha-DHTBZ (2*R*,3*R*,11b*R*-DHTBZ) were present as minor metabolites. The [+]-alpha-DHTBZ (2*R*,3*R*,11b*R*-DHTBZ) isomer was determined to be present in the least amount of all four isomers. Thus, [+]-beta-DHTBZ (2*S*,3*R*,11b*R*-DHTBZ) appears to be the major DHTBZ isomer contributing to the pharmacological activity of (±)-TBZ. Once formed, the half-life of [+]-beta-DHTBZ (2*S*,3*R*,11b*R*-DHTBZ) is relatively short (approximately 5 hours) which requires (±)-TBZ to have a sub-optimal (TID) dosing regimen.

(±)-TBZ has a narrow therapeutic window, and its clinical use requires careful dose titration. Side effects associated with (±)-TBZ and/or its metabolites include neuroleptic malignant syndrome, drowsiness, fatigue, nervousness, anxiety, insomnia, agitation, confusion, orthostatic hypotension, nausea, dizziness, sedation, depression, akathisia, and Parkinsonism. The probability of observing side effects is a function of the achieved plasma concentrations from a given dosing regimen. Compounds with a longer half-life ($t_{1/2}$) and lower clearance will have lower peak-to-trough fluctuations in plasma exposure given an equivalent dosing interval. These longer half-life compounds may exhibit improved tolerability by maintaining drug concentrations at levels needed for efficacy but below levels that may elicit side effects.

A fundamental and effective strategy to improve drug half-life is to reduce clearance. The term clearance describes the process of drug elimination from the body or from a single organ, defined as the volume of fluid cleared of drug from the body per unit of time. Clearance is a fundamental pharmacokinetic parameter and is commonly measured in drug research and development as this parameter impacts drug attributes such as half-life and, ultimately, the dosing regimen. When compound and dose selection is optimized, the benefits of small plasma-concentration fluctuations seen in compounds with low clearance include potentially reduced steady state peak concentrations, increased trough concentrations, and the prospect of improving medication adherence because of a possibly improved risk-benefit profile.

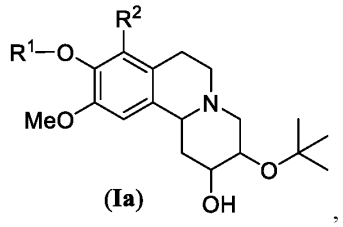
Despite the advances that have been made in this field, a need remains in the art for improved VMAT2 inhibitors, including compounds, compositions, and methods related thereto. The identification of long half-life / low clearance VMAT2 small molecule inhibitors is advantageous for drug development, particularly when being developed for chronic administration. In certain disease

populations where patient compliance and pill burden are an ongoing challenge, reduced dosing frequency is highly desirable and offers increased patient benefit.

The present disclosure fulfills these, such as, improved *in vitro* VMAT2 potency or improved pharmacokinetics, or both, and other needs, as evident in reference to the following disclosure.

SUMMARY

One aspect of the present disclosure encompasses, *inter alia*, a compound of Formula (**Ia**):



(**Ia**),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl; and

R^2 is halogen.

Also provided herein are pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound, as described herein, or a pharmaceutically acceptable salt thereof.

Also provided herein are pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound, as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Also provided herein are pharmaceutical compositions comprising a compound, as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Also provided herein are methods for preparing a pharmaceutical composition comprising the step of admixing a compound, as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Also provided herein are methods of treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder in a subject in need thereof, comprising administering to the subject a compound,

as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein.

Also provided herein are methods of treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the VMAT2 disease or disorder is selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington's disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson's/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

Also provided herein are methods of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein.

Also provided herein are methods of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the neurological or psychiatric disease or disorder is selected from: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis.

Also provided herein are methods of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.

Also provided herein are methods of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the hyperkinetic movement disorder is

selected from: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.

Also provided herein are methods of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the hyperkinetic movement disorder is tardive dyskinesia.

Also provided herein are methods of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the hyperkinetic movement disorder is Huntington's disease.

Also provided herein are methods of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.

Also provided herein are methods of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder. In some embodiments, the neurological or psychiatric disease or disorder is schizophrenia. In some embodiments, the neurological or psychiatric disease or disorder is schizoaffective disorder. In some embodiments, the neurological or psychiatric disease or disorder is obsessive-compulsive disorder. In some embodiments, the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder. In some embodiments, the neurological or psychiatric disease or disorder is autism spectrum disorder. In some embodiments, the method comprises using the compound, salt, product, or composition in adjunctive therapy.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a vesicular

monoamine transporter-2 (VMAT2) disease or disorder selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington's disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson's/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder selected from: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a hyperkinetic movement disorder.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a hyperkinetic movement disorder; wherein the hyperkinetic movement disorder is selected from: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating tardive dyskinesia.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical

composition as described herein; in the manufacture of a medicament for treating Huntington's disease.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating chorea associated with Huntington's disease.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder, wherein the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder. In some embodiments, the neurological or psychiatric disease or disorder is schizophrenia. In some embodiments, the neurological or psychiatric disease or disorder is schizoaffective disorder. In some embodiments, the neurological or psychiatric disease or disorder is obsessive-compulsive disorder. In some embodiments, the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder. In some embodiments, the neurological or psychiatric disease or disorder is autism spectrum disorder. In some embodiments, treatment comprises using the compound, salt, product, or composition in adjunctive therapy.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington’s disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson’s/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a neurological or psychiatric disease or disorder.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a neurological or psychiatric disease or disorder selected

from: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a hyperkinetic movement disorder.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a hyperkinetic movement disorder; wherein the hyperkinetic movement disorder is selected from: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating tardive dyskinesia.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating Huntington's disease.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating chorea associated with Huntington's disease.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a neurological or psychiatric disease or disorder, wherein the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder. In some embodiments, the neurological or psychiatric disease or disorder is schizophrenia. In some embodiments, the neurological or psychiatric disease or disorder is schizoaffective disorder. In some embodiments, the neurological or psychiatric disease or disorder is obsessive-compulsive disorder. In some embodiments, the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder. In some embodiments, the neurological or psychiatric disease or disorder is autism spectrum disorder. In some embodiments, the method for treating comprises using the compound, salt, product, or composition in adjunctive therapy.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a general synthetic scheme for the preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 1-9**) utilizing intermediate (±)-1-(6-(benzyloxy)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(*tert*-butoxy)propan-2-one (**Compound 1-4**) and a resolution step of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound (±)-1-6**) with

(2*S*,3*S*)-2,3-*bis*(4-methylbenzoyloxy)butanedioic acid (DPTTA) to provide (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 1-8**) that is subsequently deprotected to provide **Compound 1-9**.

FIG. 2 shows a general synthetic scheme for the preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 1-9**) utilizing intermediates 1-(*tert*-butoxy)propan-2-one (**Compound 1-20**) and 3-(*tert*-butoxy)-4-(dimethylamino)butan-2-one (**Compound 1-21**) to give (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (**Compound (±)-1-5**) that is subsequently reduced to provide (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound (±)-1-6**). A resolution step of **Compound (±)-1-6** with (2*S*,3*S*)-2,3-*bis*(4-methylbenzoyloxy)butanedioic acid (DPTTA) is utilized to provide (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 1-8**) that is subsequently deprotected to provide **Compound 1-9**.

FIG. 3 shows a general synthetic scheme for the preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 2-11**) utilizing intermediates 6-(benzyloxy)-5-fluoro-7-methoxy-3,4-dihydroisoquinoline (**Compound 2-7**) and 3-(*tert*-butoxy)-4-(dimethylamino)butan-2-one (**Compound 2-8**) to give (±)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9**). **Compound 2-9** is subsequently reduced, purified by supercritical fluid chromatography (OJ-H column) to provide (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound 2-10**) that is deprotected to give (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 2-11**).

FIG. 4 shows a general synthetic scheme for the preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 3-1**) utilizing (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 1-9**) and *N*-chlorosuccinimide (NCS), see **EXAMPLE 5** for details; and the preparation of (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 3-2**) utilizing (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 1-9**) and *N*-bromosuccinimide (NBS), see **EXAMPLE 6** for details.

FIG. 5 shows a general synthetic scheme for the preparation of compounds of Formula (**Ia**) and/or compounds of Formula (**4-2**) utilizing the 2,9-diol (**Compound 4-1**), and various alkylating agents; wherein R^1 has the same meaning as described herein, LG^1 is a Leaving Group, and R^{4a} can be H or C_1-C_4-alkyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxy. It is understood that LG^1 can be a variety of leaving groups, such as those described herein and those known in the art.

FIG. 6 shows a general synthetic scheme for the preparation of compounds of Formula **(Ia)** utilizing the 2,9-diol **(Compound 4-1)**, and different alkylating agents; wherein R^1 has the same meaning as described herein.

FIG. 7 shows a general synthetic scheme for the preparation of compounds of Formula **(Ie)** and/or compounds of Formula **(6-2)** utilizing the (2*R*,3*R*,11b*R*)-2,9-diol **(Compound 6-1)**, and various alkylating agents; wherein R^1 has the same meaning as described herein, LG^1 is a Leaving Group, and R^{4a} can be H or C_1-C_4-alkyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxy. It is understood that LG^1 can be a variety of leaving groups, such as those described herein and those known in the art.

FIG. 8 shows a general synthetic scheme for the preparation of compounds of Formula **(Ie)** utilizing the (2*R*,3*R*,11b*R*)-2,9-diol **(Compound 6-1)**, and different alkylating agents; wherein R^1 has the same meaning as described herein.

DETAILED DESCRIPTION

DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

As used herein, "**about**" means ± 20% of the stated value, and includes more specifically values of ± 10%, ± 5%, ± 2%, and ± 1% of the stated value.

The terms "**adjunctive treatment**", "**adjunctive therapy**", "**co-therapy**", "**combination therapy**", and "**combined treatment**" as used herein refers to the treatment of a patient in need thereof by administering a compound (as described herein) in combination with one or more medications, wherein the administration is by any suitable means, such as, simultaneously, sequentially, separately, or in a single pharmaceutical formulation.

The terms "**administering**" and "**administration**" as used herein refer to providing a compound described herein or other therapy to a subject in a form that can be introduced into that subject's body in a therapeutically useful form and therapeutically useful amount, including, but not limited to: oral dosage forms, such as, tablets, capsules, syrups, suspensions, and the like; injectable dosage forms, such as, intravenous (IV), intramuscular (IM), subcutaneous (SC), and the like; transdermal dosage forms, including creams, jellies, powders, and patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal dosages forms, such as, suppositories.

A health care practitioner can directly provide a compound described herein to a subject in the form of a sample or can indirectly provide a compound to a subject by providing an oral or written prescription for the compound. Also, for example, a subject can obtain a compound by themselves without the involvement of a health care practitioner. When the compound is administered to the subject, the body is transformed by the compound in some way. When a compound, as described herein, is provided in combination with one or more other agents, "administering" and

"administration" are understood to include the compound and at least one other agent are administered at the same time or at different times. When the agents of a combination are administered at the same time, they can be administered together in a single composition, or they can be administered separately. The preferred method of administration can vary depending on various factors, *e.g.*, the components of the pharmaceutical formulation, the site of the disease, and the severity of the disease.

The term "**composition**" refers to a compound or crystalline form thereof, including but not limited to, salts, solvates, and hydrates of a compound described herein, in combination with at least one additional component, such as, a composition obtained/prepared during synthesis, preformulation, in-process testing (*e.g.*, TLC, HPLC, NMR samples), and the like.

The term, "**compound**" as used herein refers to all stereoisomers, geometric isomers, tautomers, and isotopic variants of the structures depicted herein. The term is also meant to refer to compounds described herein, regardless of how they are prepared, *e.g.*, synthetically, through biological process (*e.g.*, metabolism or enzyme conversion), or a combination thereof. All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances, such as, water and solvents (*e.g.*, hydrates and solvates) or can be isolated. When in the solid state, the compounds described herein and salts thereof can occur in various forms and can, *e.g.*, take the form of co-crystals or solvates, including hydrates. The compounds can be in any solid-state form, such as, a polymorph or solvate, so unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as encompassing any solid-state form of the compound. In some embodiments, the compounds described herein, or salts thereof, are substantially isolated. By "**substantially isolated**" refers to the compound that is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, *e.g.*, a composition enriched in the compounds described herein. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds described herein, or salts thereof.

The term "**solvate**" as used herein refers to a compound, as described herein, or a pharmaceutically acceptable salt thereof, which includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. When the solvent is water, the solvate is a hydrate.

The term "**hydrate**" as used herein refers to a compound, as described herein, or a pharmaceutically acceptable salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

The term "**in need of treatment**" and the term "in need thereof" when referring to treatment are used interchangeably to mean a judgment made by a caregiver (*e.g.*, physician, nurse, nurse practitioner, *etc.* in the case of humans; veterinarian in the case of animals, including non-human

mammals) that a subject or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the subject or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compound described herein. Accordingly, the compound described herein can be used in a protective or preventive manner; or compound described herein can be used to alleviate, inhibit, or ameliorate the disease, condition, or disorder.

The term "**subject**" refers to any animal, including mammals, such as, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In the context of a clinical trial or screening or activity experiment the subject can be a healthy volunteer or healthy participant without an underlying VMAT2 mediated disorder or condition or a volunteer or participant that has received a diagnosis for a disorder or condition in need of medical treatment as determined by a health care professional. In the context outside of a clinical trial a subject under the care of a health care professional who has received a diagnosis for a disorder or condition is typically described as a subject.

The term "**pediatric subject**" refers to a subject under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)) see *e.g.*, Berhman *et al.*, Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph *et al.*, Rudolph's Pediatrics, 21st Ed. New York: McGraw-Hill, 2002; and Avery *et al.*, Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994.

The phrase "**pharmaceutically acceptable**" refers to compounds (and salts thereof), compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The term "**pharmaceutical composition**" refers to a specific composition comprising at least one active ingredient; including but not limited to, salts, solvates, and hydrates of compounds described herein, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The terms "**prevent**", "**preventing**", and "**prevention**" refer to the elimination or reduction of the occurrence or onset of one or more symptoms associated with a particular disorder. For example, the terms "prevent", "preventing", and "prevention" can refer to the administration of therapy on a prophylactic or preventative basis to a subject who may ultimately manifest at least one

symptom of a disorder but who has not yet done so. Such subjects can be identified on the basis of risk factors that are known to correlate with the subsequent occurrence of the disease, such as, the presence of a biomarker. Alternatively, prevention therapy can be administered as a prophylactic measure without prior identification of a risk factor. Delaying the onset of at least one episode and/or symptom of a disorder can also be considered prevention or prophylaxis. In some embodiments, the subject can be a pediatric subject.

The terms "**treat**", "**treating**", and "**treatment**" refer to medical management of a disease, disorder, or condition of a subject (*e.g.*, subject) (see, *e.g.*, Stedman's Medical Dictionary). In general, an appropriate dose and treatment regimen provide the VMAT2 inhibitor in an amount sufficient to provide therapeutic benefit. Therapeutic benefit for subjects to whom the VMAT2 inhibitor compound(s) described herein are administered, includes, for example, an improved clinical outcome, wherein the object is to prevent or slow or retard (lessen) an undesired physiological change associated with the disease, or to prevent or slow or retard (lessen) the expansion or severity of such disease. The effectiveness of one or more VMAT2 inhibitors can include beneficial or desired clinical results that comprise, but are not limited to, abatement, lessening, or alleviation of symptoms that result from or are associated with the disease to be treated; decreased occurrence of symptoms; improved quality of life; longer disease-free status (*i.e.*, decreasing the likelihood or the propensity that a subject will present symptoms on the basis of which a diagnosis of a disease is made); diminishment of extent of disease; stabilized (*i.e.*, not worsening) state of disease; delay or slowing of disease progression; amelioration or palliation of the disease state; and remission (whether partial or total), whether detectable or undetectable; and/or overall survival. In some embodiments, the subject can be a pediatric subject.

The term "**therapeutically effective amount**" refers to the amount of the compound described herein, or a pharmaceutically acceptable salt thereof, or an amount of a pharmaceutical composition comprising the compound described herein or a pharmaceutically acceptable salt thereof, that elicits the biological or medicinal response in a tissue, system, animal, or human that is being sought by a subject, researcher, veterinarian, medical doctor, or other clinician or caregiver, which can include one or more of the following:

(1) preventing the disorder, for example, preventing a disease, condition, or disorder in a subject who can be predisposed to the disease, condition, or disorder but does not yet experience or display the relevant pathology or symptomatology;

(2) inhibiting the disorder, for example, inhibiting a disease, condition, or disorder in a subject who is experiencing or displaying the relevant pathology or symptomatology (*i.e.*, arresting further development of the pathology and/or symptomatology); and

(3) ameliorating the disorder, for example, ameliorating a disease, condition, or disorder in a subject who is experiencing or displaying the relevant pathology or symptomatology (*i.e.*, reversing the pathology and/or symptomatology).

The term "**contacting**" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the VMAT2 protein with a compound provided herein includes the administration of a compound provided herein (or a pharmaceutically acceptable salt thereof) to a subject, such as, a human, having a VMAT2 protein, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the VMAT2 protein.

CHEMICAL GROUPS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications, and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

The term "**a-membered**" (wherein "**a**" is an integer) preceding the name of a group refers to the number of atoms in that group. For example, oxetanyl contains four atoms and is a 4-membered-heterocyclyl; and oxolanyl is an example of a 5-membered-heterocyclyl ring. Similarly, the term "a-b-membered" (wherein "**a**" and "**b**" are integers) preceding the name of a group refers to the inclusive range of atoms in that group. For example, a "**3-7-membered-heterocyclyl**" group refers to all "**heterocyclyl**" groups having from 3 to 7 atoms (*i.e.*, 3, 4, 5, 6, and 7 atoms), where "**heterocyclyl**" is defined herein; and "**4-5-membered-heterocyclyl**" refers to all "**heterocyclyl**" groups having from 4 to 5 atoms (*i.e.*, 4 and 5 atoms). If no "**a**" and "**b**" are designated to a group, the broadest range described in these definitions is to be assumed.

For compounds, as described herein, or pharmaceutically acceptable salts thereof, in which a variable appears more than once, each variable can be a different moiety independently selected from the group defining the variable. For example, where a structure is described having, for example, two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties independently selected from the group defined for R, or the two R groups can be the same.

Whenever a group is described as being "**substituted**", that group can be substituted with one or more of the indicated substituents. Likewise, when a group is described as being "**unsubstituted or substituted**" if substituted, the substituent(s) can be selected from one or more of the indicated substituents. It is to be understood that substitution at a given atom is limited by valency. Further, it is understood that "**optionally substituted**" refers to the group as being unsubstituted or substituted.

The term "**C_a-C_b**" (wherein "**a**" and "**b**" are integers) preceding the name of a group refers to the inclusive range of carbon atoms in that group. For example, a "**C_1-C_4-alkyl**" group refers to all alkyl groups having from 1 to 4 carbons (*i.e.*, 1, 2, 3, and 4 carbons), such as, methyl (CH_3-), ethyl (CH_3CH_2-), *n*-propyl ($CH_3CH_2CH_2$-), *iso*-propyl ($(CH_3)_2CH$-), *n*-butyl ($CH_3CH_2CH_2CH_2$-), *iso*-butyl

($(CH_3)_2CHCH_2$-), *sec*-butyl ($CH_3CH_2CH(CH_3)$-), and *tert*-butyl ($(CH_3)_3C$-). If no "**a**" and "**b**" are designated with regard to a group, the broadest range described in these definitions is to be assumed.

In addition to the foregoing, as used in the specification and claims, unless specified to the contrary, the following terms have the meaning indicated.

The terms "**C_1-C_4-alkylene**" and "**C_2-C_4-alkylene**" refers to a straight or branched, saturated aliphatic, divalent radical having the defined number of carbons, 1 to 4 carbon atoms or 2 to 4 carbon atoms respectively. Some embodiments contain 1 to 2 carbons. Some embodiments contain 1 to 3 carbons. Some embodiments contain 1 carbon atom. Some embodiments contain 2 to 3 carbons. Some embodiments contain 2 carbon atoms. Examples include, but are not limited to, methylene (*i.e.*, $-CH_2-$), ethylene (*i.e.*, $-CH_2CH_2-$ and $-CH(CH_3)-$), *n*-propylene, isopropylene, *n*-butylene, *s*-butylene, isobutylene, and *t*-butylene. When one or more substituents are present on the "**alkylene**" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**alkylene**" group can be substituted or unsubstituted.

The term "**C_1-C_4-alkyl-O-C_2-C_4-alkylene**" refers to a radical group consisting of a "**C_1-C_4-alkyl**" group bonded to an oxygen atom and the oxygen atom is bonded to a "**C_2-C_4 alkylene**" radical, wherein "**C_1-C_4-alkyl**" and "**C_2-C_4 alkylene**" have the same definitions as described herein. Examples include, but are not limited to, 1-methoxyethyl (*i.e.*, CH_3-O-$CH(CH_3)$-), 2-methoxyethyl (*i.e.*, CH_3-O-CH_2CH_2-), 2-ethoxyethyl, 2-propoxyethyl, 2-isopropoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, 3-propoxypropyl, and 3-isopropoxypropyl. In some embodiments, "**C_1-C_4-alkyl-O-C_2-C_4-alkylene**" refers to a group selected from: 2-methoxyethyl (*i.e.*, CH_3-O-CH_2CH_2-), 2-ethoxyethyl, 2-propoxyethyl, 2-isopropoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, 3-propoxypropyl, and 3-isopropoxypropyl. When one or more substituents are present on the "**C_1-C_4-alkyl-O-C_2-C_4-alkylene**" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**C_1-C_4-alkyl-O-C_2-C_4-alkylene**" group can be substituted or unsubstituted.

The term "**alkoxy**" refers to a radical comprising an "**alkyl**" group attached directly to an oxygen atom, wherein "**alkyl**" has the same definition as found herein. Some embodiments contain 1 to 4 carbons (*i.e.*, "**C_1-C_4-alkoxy**"). Some embodiments contain 1 to 3 carbons (*i.e.*, "**C_1-C_3-alkoxy**"). Some embodiments contain 1 or 2 carbons. Examples include, but are not limited to, methoxy, ethoxy, *n*-propoxy, 1-methylethoxy (*iso*-propoxy), *n*-butoxy, *iso*-butoxy, *sec*-butoxy, and *tert*-butoxy.

The term "**alkyl**" refers to a fully saturated straight or branched hydrocarbon radical. In some embodiments, the alkyl group can have 1 to 6 carbons (*i.e.*, "**C_1-C_6-alkyl**"). Some embodiments are 1 to 5 carbons (*i.e.*, "**C_1-C_5-alkyl**"), some embodiments are 1 to 4 carbons (*i.e.*, "**C_1-C_4-alkyl**"), some embodiments are 1 to 3 carbons (*i.e.*, "**C_1-C_3-alkyl**"), and some embodiments are 1 or 2 carbons. By way of example only, "**C_1-C_4-alkyl**" indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from methyl, methyl-d_3, ethyl, ethyl-d_5, *n*-propyl, *iso*-propyl, *n*-

butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl. Examples include, but are not limited to, methyl, methyl-d_3, ethyl, ethyl-d_5, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, pentyl, *iso*-pentyl, *tert*-pentyl, *neo*-pentyl, 1-methylbutyl [*i.e.*, -$CH(CH_3)CH_2CH_2CH_3$], 2-methylbutyl [*i.e.*, -$CH_2CH(CH_3)CH_2CH_3$], and *n*-hexyl. When one or more substituents are present on the "**alkyl**" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**alkyl**" group can be substituted or unsubstituted.

The term "**bicycloalkyl**" refers to a radical comprising two fused or bridged cycloalkyl rings. In some embodiments, the "**bicycloalkyl**" group contains 4 to 8 ring carbon atoms. In some embodiments, the "**bicycloalkyl**" group contains 5 to 8 ring carbon atoms. In some embodiments, the "bicycloalkyl" group contains 5 to 7 ring carbon atoms. In some embodiments, the "**bicycloalkyl**" group contains 5 or 6 ring carbon atoms. Examples include, but are not limited to, bicyclo[1.1.0]butanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]heptyl, and bicyclo[3.2.1]octyl. When one or more substituents are present on the "bicycloalkyl" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**bicycloalkyl**" group can be substituted or unsubstituted.

The term "**C_4-C_8-bicycloalkyl-C_1-C_4-alkylene**" refers to a radical group consisting of a "**C_4-C_8-bicycloalkyl**" group bonded to a "**C_1-C_4 alkylene**" radical, wherein "**C_4-C_8-bicycloalkyl**" and "**C_1-C_4 alkylene**" have the same definitions as described herein. Examples include, but are not limited to, (bicyclo[1.1.0]butan-1-yl)methyl (*i.e.*, (bicyclo[1.1.0]butan-1-yl)CH_2-), (bicyclo[1.1.1]pentan-1-yl)methyl (*i.e.*, (bicyclo[1.1.1]pentan-1-yl)CH_2-), (bicyclo[2.2.1]hex-1-yl)methyl, (bicyclo[2.2.1]hept-1-yl)methyl, and (bicyclo[2.2.2]oct-1-yl)methyl. When one or more substituents are present on the "**C_4-C_8-bicycloalkyl-C_1-C_4-alkylene**" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**C_4-C_8-bicycloalkyl-C_1-C_4-alkylene**" group can be substituted or unsubstituted.

The term "**4-8-membered-heterobicyclyl**" refers to a radical comprising two fused or bridged rings comprising carbon atoms and at least one heteroatom. The heteroatom(s) include, but are not limited to, oxygen, sulfur, and nitrogen, when more than one heteroatom is present in the ring the heteroatoms can be the same or different. In some embodiments, the "**4-8-membered-heterobicyclyl**" is a group selected from: 2-oxabicyclo[2.1.1]hexan-1-yl and 2-oxabicyclo[2.1.1]hexan-4-yl. When one or more substituents are present on the "**4-8-membered-heterobicyclyl**" group, the substituent(s) can be bonded at any available ring atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**4-8-membered-heterobicyclyl**" group can be substituted or unsubstituted.

The term "**carbonyl**" refers to the group -C(=O)-.

The term "**cyano**" refers to the group -CN.

The term "**cycloalkyl**" refers to a fully saturated, all carbon, monocyclic ring system. In some embodiments, the cycloalkyl is a monocyclic ring containing 3 to 7 carbon atoms (*i.e.*, "**C_3-C_7-cycloalkyl**"). Some embodiments contain 3 to 6 carbons (*i.e.*, "**C_3-C_6-cycloalkyl**"). Some embodiments contain 3 to 5 carbons. Some embodiments contain 5 to 7 carbons. Some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. When one or more substituents are present on the "cycloalkyl" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**cycloalkyl**" group can be substituted or unsubstituted.

The term "**C_3-C_7-cycloalkyl-C_1-C_4-alkylene**" refers to a radical group consisting of a "**C_3-C_7-cycloalkyl**" group bonded to a "**C_1-C_4 alkylene**" radical, wherein "**C_3-C_7-cycloalkyl**" and "**C_1-C_4 alkylene**" have the same definitions as described herein. Examples include, but are not limited to, cyclopropylmethyl (cyclopropyl-CH_2-), (cyclopropyl)methyl-d_2, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, 2-cyclopropylethyl (cyclopropyl-CH_2CH_2-), 2-cyclobutylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 2-cycloheptylethyl, 1-cyclopropylethyl (cyclopropyl-$CH(CH_3)$-), 1-cyclobutylethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 1-cycloheptylethyl, 3-cyclopropylpropyl, 3-cyclobutylpropyl, 3-cyclopentylpropyl, 3-cyclohexylpropyl, 3-cycloheptylpropyl, 4-cyclopropylbutyl, 4-cyclobutylbutyl, 4-cyclopentylbutyl, 4-cyclohexylbutyl, and 4-cycloheptylbutyl. It is understood that the chemical group "(cyclopropyl)methyl-d_2" refers to the group in which the deuterium atoms are bonded to the methylene carbon (*i.e.*, cyclopropyl-CD_2-), for example, see **Compound 68**. When one or more substituents are present on the "C_3-C_7-cycloalkyl-C_1-C_4-alkylene" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**C_3-C_7-cycloalkyl-C_1-C_4-alkylene**" group can be substituted or unsubstituted.

The term "**C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene**" refers to a radical group consisting of a "**C_3-C_7-cycloalkyl**" group bonded to an oxygen atom and the oxygen atom is bonded to a "**C_2-C_4 alkylene**" radical, wherein "**C_3-C_7-cycloalkyl**" and "**C_2-C_4 alkylene**" have the same definitions as described herein. Examples include, but are not limited to, 2-cyclopropoxyethyl (*i.e.*, cyclopropyl-O-CH_2CH_2-), 2-cyclobutoxyethyl, 2-cyclopentyloxyethyl, 2-cyclohexyloxyethyl, 2-cycloheptyloxyethyl, 1-cyclopropoxyethyl (*i.e.*, cyclopropyl-O-$CH(CH_3)$-), 1-cyclobutoxyethyl, 1-cyclopentyloxyethyl, 1-cyclohexyloxyethyl, 1-cycloheptyloxyethyl, 3-cyclopropoxypropyl, 3-cyclobutoxypropyl, 3-cyclopentyloxypropyl, 3-cyclohexyloxypropyl, and 3-cycloheptyloxypropyl. When one or more substituents are present on the "**C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene**" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene**" group can be substituted or unsubstituted.

The term "**haloalkyl**" refers to an alkyl group, as defined herein, wherein one or more hydrogen atoms of the alkyl group have been replaced by a halogen atom. In some embodiments, the haloalkyl group can have 1 to 6 carbons (*i.e.*, "**C_1-C_6-haloalkyl**"). The haloC_1-C_6alkyl can be fully substituted in which case it can be represented by the formula C_nL_{2n+1}, wherein L is a halogen and "**n**" is 1, 2, 3, 4, 5, or 6. When more than one halogen is present then they can be the same or different and selected from: fluorine, chlorine, bromine, and iodine. In some embodiments, haloalkyl contains 1 to 5 carbons (*i.e.*, "**C_1-C_5-haloalkyl**"). In some embodiments, haloalkyl contains 1 to 4 carbons (*i.e.*, "**C_1-C_4-haloalkyl**"). In some embodiments, haloalkyl contains 1 to 3 carbons (*i.e.*, "**C_1-C_3-haloalkyl**"). In some embodiments, haloalkyl contains 1 or 2 carbons. Examples include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 1-fluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, and 4,4,4-trifluorobutyl.

The term "**halogen**" or "**halo**" refers to the fluoro (F), chloro (Cl), bromo (Br), or iodo (I) group. In some embodiments, halogen or halo is fluoro, chloro, or bromo. In some embodiments, halogen or halo is fluoro or chloro. In some embodiments, halogen or halo is fluoro.

The term "**heterocyclyl**" refers to a non-aromatic monocyclic ring system containing carbon atoms and at least one heteroatom. The heteroatom(s) include, but not limited to, oxygen, sulfur, and nitrogen, when more than one heteroatom is present in the ring the heteroatoms can be the same or different. In some embodiments, "**3-7-membered-heterocyclyl**" refers to a ring system containing 3 to 7 ring atoms, wherein at least one ring atom is a heteroatom. In some embodiments, "**4-5-membered-heterocyclyl**" refers to a ring system containing 4 or 5 ring atoms, wherein at least one ring atom is a heteroatom. In some embodiments, "**4-7-membered-heterocyclyl**" refers to a ring system containing 4 to 7 ring atoms, wherein at least one ring atom is a heteroatom. In some embodiments, "**3-6-membered-heterocyclyl**" refers to a ring system containing 3 to 6 ring atoms, wherein at least one ring atom is a heteroatom. In some embodiments, "**4-6-membered-heterocyclyl**" refers to a ring system containing 4 to 6 ring atoms, wherein at least one ring atom is a heteroatom. In some embodiments, the one or two heteroatoms in the ring system are selected independently from: O (oxygen) and N (nitrogen). In some embodiments, a heterocyclyl can include a carbonyl (C=O) group adjacent to a hetero atom, that is, be substituted with an oxo on a carbon adjacent to a hetero atom, where the substituted ring system is a lactam, lactone, cyclic imide, cyclic thioimide, or cyclic carbamate. Examples include, but are not limited to, aziridinyl, azetidinyl, piperidinyl, morpholinyl, oxetanyl, oxolanyl, imidazolidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, and tetrahydrothiopyranyl. When one or more substituents are present on the "**heterocyclyl**" group, the substituent(s) can be bonded at any available carbon atom and/or heteroatom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**heterocyclyl**" group can be substituted or unsubstituted.

The term "**4-8-membered-heterobicyclyl-C_1-C_4-alkylene**" refers to a radical group consisting of a "**4-8-membered-heterobicyclyl**" group bonded to a "**C_1-C_4 alkylene**" radical,

wherein "**4-8-membered-heterobicyclyl**" and "**C_1-C_4 alkylene**" have the same definitions as described herein. In some embodiments, the "**4-8-membered-heterobicyclyl-C_1-C_4-alkylene**" is a group selected from: (2-oxabicyclo[2.1.1]hexan-1-yl)methyl and (2-oxabicyclo[2.1.1]hexan-4-yl)methyl. When one or more substituents are present on the "**4-8-membered-heterobicyclyl-C_1-C_4-alkylene**" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**4-8-membered-heterobicyclyl-C_1-C_4-alkylene**" group can be substituted or unsubstituted.

The term "**3-7-membered-heterocyclyl-C_1-C_4-alkylene**" refers to a radical group consisting of a "**3-7-membered-heterocyclyl**" group bonded to a "**C_1-C_4 alkylene**" radical, wherein "**3-7-membered-heterocyclyl**" and "**C_1-C_4 alkylene**" have the same definitions as described herein. Examples include, but are not limited to, aziridin-1-ylmethyl(*i.e.*, (aziridin-1-yl)CH_2-), aziridin-2-ylmethyl, azetidin-2-ylmethyl (*i.e.*, (azetidin-2-yl)CH_2-), azetidin-3-ylmethyl (*i.e.*, (azetidin-3-yl)CH_2-), piperidinylmethyl, morpholinyl, oxetan-3-ylmethyl (*i.e.*, (oxetan-3-yl)CH_2-), oxetan-2-ylmethyl (*i.e.*, (oxetan-2-yl)CH_2-), 2-oxetan-3-ylethyl (*i.e.*, (oxetan-3-yl)CH_2CH_2-), 2-oxetan-2-ylethyl (*i.e.*, (oxetan-2-yl)CH_2CH_2-), imidazolidinylmethyl, piperazin-1-ylmethyl, piperazin-2-ylmethyl, pyrrolidin-3-ylmethyl, tetrahydrofuranylmethyl, tetrahydropyranylmethyl, and tetrahydrothiopyranylmethyl. In some embodiments, "**3-7-membered-heterocyclyl-C_1-C_4-alkylene**" is a group selected from: oxetan-3-ylmethyl (*i.e.*, (oxetan-3-yl)CH_2-), oxetan-2-ylmethyl (*i.e.*, (oxetan-2-yl)CH_2-), 2-oxetan-3-ylethyl (*i.e.*, (oxetan-3-yl)CH_2CH_2-), and 2-oxetan-2-ylethyl (*i.e.*, (oxetan-2-yl)CH_2CH_2-). When one or more substituents are present on the "**3-7-membered-heterocyclyl-C_1-C_4-alkylene**" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**3-7-membered-heterocyclyl-C_1-C_4-alkylene**" group can be substituted or unsubstituted.

The term "**spiro-cycloalkyl**" refers to a non-aromatic, all carbon, bicyclic ring system where both rings are linked together by a single common ring carbon. In some embodiments, "**C_5-C_{11}-spiro-cycloalkyl**" refers to a spiro ring system containing 5 to 11 ring carbons. In some embodiments, "**C_5-C_8-spiro-cycloalkyl**" refers to a spiro ring system containing 5 to 8 ring carbons. In some embodiments, "**C_5-C_7-spiro-cycloalkyl**" refers to a spiro ring system containing 5 to 7 ring carbons. In some embodiments, "**C_7-spiro-cycloalkyl**" refers to a spiro ring system containing 7 ring carbons (*i.e.*, spiro[3.3]heptanyl and spiro[2.4]heptanyl). Examples include, but are not limited to, spiro[2.2]pentanyl, spiro[2.3]hexanyl, spiro[3.3]heptanyl, spiro[2.4]heptanyl, spiro[2.5]octanyl, spiro[3.4]octanyl, spiro[2.6]nonanyl, spiro[3.5]nonanyl, spiro[4.4]nonanyl, spiro[2.7]decanyl, spiro[3.6]decanyl, and spiro[4.5]decanyl. When one or more substituents are present on the "**spiro-cycloalkyl**" group, the substituent(s) can be bonded at any available carbon atom. When more than one substituent is present, the substituents can be the same or different. In some embodiments, the "**spiro-cycloalkyl**" group can be substituted or unsubstituted.

The term "**hydroxyl**" refers to the group -OH.

As used herein, an "**excipient**" refers to a substance that is added to a composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability, *etc.*, to the composition. A "**diluent**" is a type of excipient and refers to an ingredient in a pharmaceutical composition that lacks pharmacological activity but can be pharmaceutically necessary or desirable. For example, a diluent can be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It can also be a liquid for the dissolution of a drug to be administered by injection, ingestion, or inhalation. A pharmaceutically acceptable excipient is a physiologically and pharmaceutically suitable non-toxic and inactive material or ingredient that does not interfere with the activity of the drug substance. Pharmaceutically acceptable excipients are well known in the pharmaceutical art and described, for example, in Rowe *et al.*, Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5th Ed., 2006, and in Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)). Preservatives, stabilizers, dyes, buffers, and the like can be provided in the pharmaceutical composition. One skilled in this art can further formulate a compound as disclosed and described herein in an appropriate manner, and in accordance with accepted practices, such as, those disclosed in Remington, *supra*.

As used herein, a "**dose**" or "**dosage**" refers to the measured quantity of drug substance to be taken at one time by a subject. In certain embodiments, wherein the drug substance is not a free base or free acid, the quantity is the molar equivalent to the corresponding amount of free base or free acid.

As used herein, a "**pharmaceutically acceptable salt**" refers to a salt of a compound having an acidic or basic moiety which is not biologically or otherwise undesirable for use in a pharmaceutical product. In many cases, the compounds disclosed herein are capable of forming acid and/or base salts by virtue of the presence of an acidic or basic moiety (*e.g.*, amino and/or carboxyl groups or groups similar thereto). Pharmaceutically acceptable acid addition salts can be formed by combining a compound having a basic moiety with inorganic acids and organic acids. Pharmaceutically acceptable base addition salts can be formed by combining a compound having an acidic moiety with inorganic and organic bases.

The compounds described herein can have one or more stereocenters. All stereoisomers, such as, enantiomers and diastereomers, are intended unless otherwise indicated. It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center can independently be the (*R*)-configuration, or the (*S*)-configuration, or a mixture thereof. Thus, the compounds provided herein can be enantiomerically pure, enantiomerically enriched, a racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. Preparation of enantiomerically pure or enantiomerically enriched forms can be accomplished by resolution of racemic mixtures or by using enantiomerically pure or enriched starting materials or by stereoselective or stereospecific synthesis. Stereochemical definitions are available in E.L. Eliel, S.H. Wilen & L.N. Mander, Stereochemistry of Organic

Compounds, John Wiley & Sons, Inc., New York, NY, 1994 which is incorporated herein by reference in its entirety. In some embodiments, where the compound described herein is chiral or otherwise includes one or more stereocenters, the compound can be prepared with an enantiomeric excess or diastereomeric excess of greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 99%, greater than about 99.5%, or greater than about 99.9%.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a chiral resolving organic acid with a racemic compound containing a basic group. Other chiral resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, *N*-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like. Similarly, fractional recrystallization using a chiral resolving base can be utilized with a racemic compound containing a basic group.

Resolution of racemic mixtures can also be carried out by elution on a chiral column. A suitable elution solvent composition can be determined by one skilled in the art.

In some embodiments, a compound described herein can be prepared having at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, at least about 99.5%, or at least about 99.9% enantiomeric excess, or an enantiomeric excess within a range defined by any of the preceding numbers. In some embodiments, a compound described herein can be prepared having at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, at least 99.5%, or at least 99.9% enantiomeric excess, or an enantiomeric excess within a range defined by any of the preceding numbers.

In some embodiments, a compound described herein can be prepared having at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, at least about 99.5%, or at least about 99.9% diastereomeric excess, or a diastereomeric excess within a range defined by any of the preceding numbers. In some embodiments, a compound described herein can be prepared having at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, at least 99.5%, or at least 99.9% diastereomeric excess, or a diastereomeric excess within a range defined by any of the preceding numbers.

In addition, it is understood that, when a compound described herein contain one or more double bond(s) (*e.g.*, C=C, C=N, and the like) or other centers of geometric asymmetry, and unless specified otherwise, it is understood that the compound includes both Z and E geometric isomers (*e.g.*,

cis or *trans*). *Cis* and *trans* geometric isomers of the compounds, as described herein, can be isolated as a mixture of isomers, or as separated isomeric form.

The compounds described herein also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1*H*- and 3*H*-imidazole, 1*H*-, 2*H*-, and 4*H*-1,2,4-triazole, 1*H*- and 2*H*-isoindole, and 1*H*- and 2*H*-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

The compounds described herein, and their pharmaceutically acceptable salts, can be found together with other substances, such as, water and solvents, for example, in the form of hydrates or solvates. When in the solid-state, the compounds described herein and salts thereof can occur in various forms and can, *e.g.*, take the form of solvates, including hydrates. The compounds can be in any solid-state form, such as, a crystalline form, amorphous form, solvated form, *etc.* and unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as reading on any solid-state form of the compound.

The compounds described herein can be used in a neutral form, such as, a free acid or free base form. Alternatively, the compounds can be used in the form of pharmaceutically acceptable salts, such as, pharmaceutically acceptable addition salts of acids or bases.

In some embodiments, the compounds described herein, or salts thereof, are substantially isolated. The phrase "substantially isolated" refers to the compound that is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound described herein. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound described herein, or salt thereof.

ISOTOPES

The compounds disclosed and described herein allow and embrace atoms at each position of the compound independently to have: 1) an isotopic distribution for a chemical element in proportional amounts to those usually found in nature or 2) an isotopic distribution in proportional amounts different to those usually found in nature unless the context clearly dictates otherwise. A particular chemical element has an atomic number defined by the number of protons within the atom's nucleus. Each atomic number identifies a specific chemical element, but not the isotope; an atom of a

given element can have a wide range in its number of neutrons. The number of both protons and neutrons in the nucleus is the atom's mass number, and each isotope of a given element has a different mass number. Compounds wherein one or more atoms have an isotopic distribution for a chemical element in proportional amounts different to those usually found in nature is commonly referred to as being isotopically-labeled. Each chemical element as represented in a compound structure can include any isotopic distribution of said element. For example, in a compound structure a hydrogen atom can be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom can be present, the hydrogen atom can be an isotopic distribution of hydrogen, including but not limited to protium (^{1}H) and deuterium (^{2}H) in proportional amounts to those usually found in nature and in proportional amounts different to those usually found in nature. Thus, reference herein to a compound encompasses all potential isotopic distributions for each atom unless the context clearly dictates otherwise. Examples of isotopes include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, bromine, and iodine. As one of skill in the art would appreciate, any of the compounds as disclosed and described herein can include radioactive isotopes. Accordingly, also contemplated is use of compounds as disclosed and described herein, wherein one or more atoms have an isotopic distribution different to those usually found in nature, such as, having ^{2}H or ^{3}H in greater proportion, or ^{11}C, ^{13}C, or ^{14}C in greater proportion than found in nature. By way of general example, and without limitation, isotopes of hydrogen include protium (^{1}H), deuterium (^{2}H), and tritium (^{3}H). Isotopes of carbon include carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), and carbon-14 (^{14}C). Isotopes of nitrogen include nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), and nitrogen-15 (^{15}N). Isotopes of oxygen include oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), and oxygen-18 (^{18}O). Isotopes of fluorine include fluorine-17 (^{17}F), fluorine-18 (^{18}F), and fluorine-19 (^{19}F). Isotopes of phosphorus include phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), phosphorus-34 (^{34}P), phosphorus-35 (^{35}P), and phosphorus-36 (^{36}P). Isotopes of sulfur include sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), and sulfur-38 (^{38}S). Isotopes of chlorine include chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), and chlorine-37 (^{37}Cl). Isotopes of bromine include bromine-75 (^{75}Br), bromine-76 (^{76}Br), bromine-77 (^{77}Br), bromine-79 (^{79}Br), bromine-81 (^{81}Br), and bromine-82 (^{82}Br). Isotopes of iodine include iodine-123 (^{123}I), iodine-124 (^{124}I), iodine-125 (^{125}I), iodine-131 (^{131}I), and iodine-135 (^{135}I). In some embodiments, atoms at every position of the compound have an isotopic distribution for each chemical element in proportional amounts to those usually found in nature. In some embodiments, an atom in one position of the compound has an isotopic distribution for a chemical element in proportional amounts different to those usually found in nature (remainder atoms having an isotopic distribution for a chemical element in proportional amounts to those usually found in nature). In some embodiments, atoms in at least two positions of the compound independently have an isotopic distribution for a chemical element in proportional amounts different to those usually found in nature (remainder atoms having an isotopic distribution for a chemical element in proportional amounts to those usually found in

nature). In some embodiments, atoms in at least three positions of the compound independently have an isotopic distribution for a chemical element in proportional amounts different to those usually found in nature (remainder atoms having an isotopic distribution for a chemical element in proportional amounts to those usually found in nature). In some embodiments, atoms in at least four positions of the compound independently have an isotopic distribution for a chemical element in proportional amounts different to those usually found in nature (remainder atoms having an isotopic distribution for a chemical element in proportional amounts to those usually found in nature). In some embodiments, atoms in at least five positions of the compound independently have an isotopic distribution for a chemical element in proportional amounts different to those usually found in nature (remainder atoms having an isotopic distribution for a chemical element in proportional amounts to those usually found in nature). In some embodiments, atoms in at least six positions of the compound independently have an isotopic distribution for a chemical element in proportional amounts different to those usually found in nature (remainder atoms having an isotopic distribution for a chemical element in proportional amounts to those usually found in nature).

Certain compounds, for example those having incorporated radioactive isotopes, such as, ^{3}H and ^{14}C, are also useful in drug or substrate tissue distribution assays. Tritium (^{3}H) and carbon-14 (^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Compounds with isotopes, such as, deuterium (^{2}H), in proportional amounts greater than usually found in nature can afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Isotopically-labeled compounds can generally be prepared by performing procedures routinely practiced in the chemical art. Methods are readily available to measure such isotope perturbations or enrichments, such as, mass spectrometry, and for isotopes that are radio-isotopes additional methods are available, such as, radio-detectors used in connection with HPLC or GC.

As used herein, "**isotopic variant**" means a compound that contains an unnatural proportion of an isotope at one or more of the atoms that constitute such a compound. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, protium (^{1}H), deuterium (^{2}H), tritium (^{3}H), carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-127 (^{127}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, an "**isotopic variant**" of a compound is in a stable form, that is, non-radioactive. In certain embodiments, an "**isotopic variant**" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), carbon-12 (^{12}C), carbon-13 (^{13}C), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N),

oxygen-16 (^{16}O), oxygen-17 (^{17}O), and oxygen-18 (^{18}O). In certain embodiments, an "**isotopic variant**" of a compound is in an unstable form, that is, radioactive. In certain embodiments, an "**isotopic variant**" of a compound described herein contains unnatural proportions of one or more isotopes, including, but not limited to, tritium (^{3}H), carbon-11 (^{11}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), oxygen-14 (^{14}O), and oxygen-15 (^{15}O). It will be understood that, in a compound as provided herein, any hydrogen can include ^{2}H as the major isotopic form, as example, or any carbon include be ^{13}C as the major isotopic form, as example, or any nitrogen can include ^{15}N as the major isotopic form, as example, and any oxygen can include ^{18}O as the major isotopic form, as example. In certain embodiments, an "**isotopic variant**" of a compound contains an unnatural proportion of deuterium (^{2}H).

With regard to the compounds provided herein, when a particular atomic position is designated as having deuterium or "D" or "d", it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of, in certain embodiments, at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium position. Similarly, with regard to the compounds provided herein when any atomic position is designated as a specific isotope, it is understood that the abundance of the specific isotope at that position is substantially greater than the natural abundance of that isotope. A position designated as having a specific isotope typically has a minimum isotopic enrichment factor of, in certain embodiments, at least 52.5%, at least 60%, at least 67.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, at least 97%, at least 99%, or at least 99.5% incorporation of the isotope at each designated position.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compound described herein and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, are as follows:

A. Catalytic Reduction with Tritium Gas: This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [^{3}H]: This procedure is rather inexpensive and requires precursors containing reducible functional groups, such as, aldehydes, ketones, lactones, esters, and the like.

C. Reduction with Lithium Aluminum Hydride [^{3}H]: This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups, such as, aldehydes, ketones, lactones, esters, and the like.

D. Tritium Gas Exposure Labeling: This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. *N*-Methylation using Methyl Iodide [^{3}H]: This procedure is usually employed to prepare O-methyl or *N*-methyl (^{3}H) products by treating appropriate precursors with high specific activity methyl iodide (^{3}H). This method in general allows for higher specific activity, such as, for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of ^{125}I into target molecules include:

A. Sandmeyer and like reactions: This procedure transforms an aryl amine or a heteroaryl amine into a diazonium salt, such as, a diazonium tetrafluoroborate salt and subsequently to ^{125}I labeled compound using Na^{125}I. A representative procedure was reported by Zhu, G-D. and co-workers in J. Org. Chem., 2002, 67, 943-948.

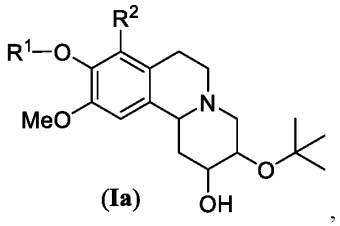
B. Ortho ^{125}Iodination of phenols: This procedure allows for the incorporation of ^{125}I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in J. Labelled Compd. Radiopharm., 1999, 42, S264-S266.

C. Aryl and heteroaryl bromide exchange with ^{125}I: This method is generally a two-step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [*i.e.* $Pd(Ph_3P)_4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [*e.g.*, $(CH_3)_3SnSn(CH_3)_3$]. A representative procedure was reported by Le Bas, M.-D. and co-workers in J. Labelled Compd. Radiopharm., 2001, 44, S280-S282.

A radiolabeled form of a compound described herein can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (*i.e.*, test compound) can be evaluated for its ability to reduce binding of a radiolabeled form of a compound disclosed herein to VMAT2. The ability of a test compound to compete with a radiolabeled form of a compound described herein for the binding to VMAT2 correlates to its binding affinity.

COMPOUNDS

One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula (**Ia**):



(Ia),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

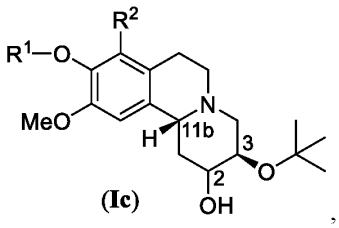
wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl; and

R^2 is halogen.

In some embodiments, the R^1 group is optionally substituted with one, two, three, four, five, six, seven, or eight substituents. In some embodiments, the R^1 group is optionally substituted with one, two, three, four, five, six, or seven substituents. In some embodiments, the R^1 group is optionally substituted with one, two, three, four, five, or six substituents. In some embodiments, the R^1 group is optionally substituted with one, two, three, four, or five substituents. In some embodiments, the R^1 group is optionally substituted with one, two, three, or four substituents. In some embodiments, the R^1 group is optionally substituted with one, two, or three substituents. In some embodiments, the R^1 group is optionally substituted with one or two substituents. In some embodiments, the R^1 group is optionally substituted with one substituent. In some embodiments, the R^1 group is not substituted.

In some embodiments, the R^1 group is substituted with one, two, three, four, five, six, seven, or eight substituents. In some embodiments, the R^1 group is substituted with one, two, three, four, five, six, or seven substituents. In some embodiments, the R^1 group is substituted with one, two, three, four, five, or six substituents. In some embodiments, the R^1 group is substituted with one, two, three, four, or five substituents. In some embodiments, the R^1 group is substituted with one, two, three, or four substituents. In some embodiments, the R^1 group is substituted with one, two, or three substituents. In some embodiments, the R^1 group is substituted with one or two substituents. In some embodiments, the R^1 group is substituted with one substituent.

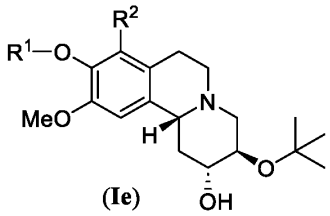
One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula (**Ic**):



(**Ic**),

or a pharmaceutically acceptable salt thereof, wherein: R^1 and R^2 have the same definitions as described herein, *supra,* and *infra*. It is understood that the stereochemistry for compounds of Formula (**Ic**) includes both the 2*S*,3*R*,11b*R* isomers and the 2*R*,3*R*,11b*R* isomers.

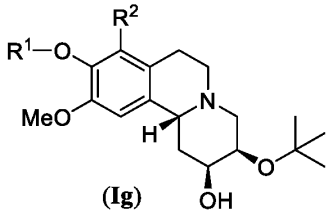
One aspect of the present disclosure encompasses, *inter alia*, compounds of (**Ie**):



(Ie),

or a pharmaceutically acceptable salt thereof, wherein: R^1 and R^2 have the same definitions as described herein, *supra,* and *infra*. The stereochemistry for a compound of Formula **(Ie)** is the 2*R*,3*R*,11b*R* isomer.

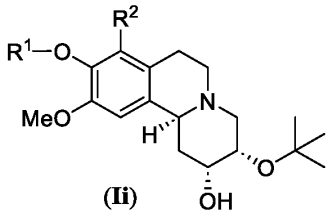
One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula **(Ig)**:



(Ig),

or a pharmaceutically acceptable salt thereof, wherein: R^1 and R^2 have the same definitions as described herein, *supra,* and *infra*. The stereochemistry for a compound of Formula **(Ig)** is the 2*S*,3*R*,11b*R* isomer.

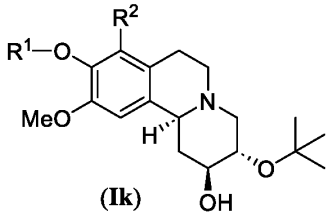
One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula **(Ii)**:



(Ii),

or a pharmaceutically acceptable salt thereof, wherein: R^1 and R^2 have the same definitions as described herein, *supra,* and *infra*. The stereochemistry for a compound of Formula **(Ii)** is the 2*R*,3*S*,11b*S* isomer.

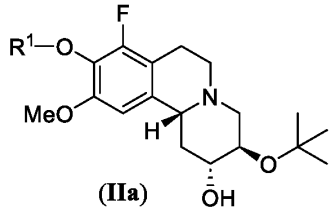
One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula **(Ik)**:



(Ik),

or a pharmaceutically acceptable salt thereof, wherein: R^1 and R^2 have the same definitions as described herein, *supra,* and *infra*. The stereochemistry for a compound of Formula **(Ik)** is the 2*S*,3*S*,11b*S* isomer.

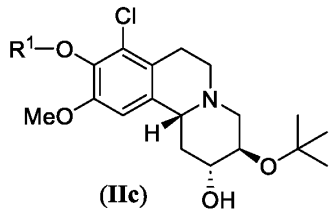
One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula (**IIa**):



(**IIa**)

or a pharmaceutically acceptable salt thereof, wherein: R^1 has the same definition as described herein, *supra,* and *infra*. The stereochemistry for a compound of Formula (**IIa**) is the 2*R*,3*R*,11b*R* isomer.

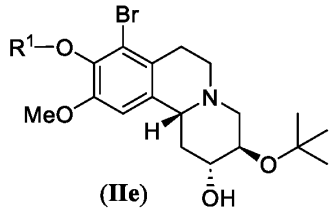
One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula (**IIc**):



(**IIc**)

or a pharmaceutically acceptable salt thereof, wherein: R^1 has the same definition as described herein, *supra,* and *infra*. The stereochemistry for a compound of Formula (**IIc**) is the 2*R*,3*R*,11b*R* isomer.

One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula (**IIe**):



(**IIe**)

or a pharmaceutically acceptable salt thereof, wherein: R^1 has the same definition as described herein, *supra,* and *infra*. The stereochemistry for a compound of Formula (**IIe**) is the 2*R*,3*R*,11b*R* isomer.

The K_i value for a compound, as described herein, or a pharmaceutically acceptable salt thereof, against VMAT2 can be determined using the assay as described in **EXAMPLE 20**. Some embodiments provide a compound, as described herein, or a pharmaceutically acceptable salt thereof, wherein the compound has a K_i value of about 50 nM or less. In some embodiments, the compound has a K_i value of about 25 nM or less. In some embodiments, the compound has a K_i value of about 25 nM or less.In some embodiments, the compound has a K_i value of about 20 nM or less. In some embodiments, the compound has a K_i value of about 15 nM or less. In some embodiments, the compound has a K_i value of about 10 nM or less. In some embodiments, the compound has a K_i value of about 9 nM or less. In some embodiments, the compound has a K_i value of about 8 nM or less. In

some embodiments, the compound has a K_i value of about 7 nM or less. In some embodiments, the compound has a K_i value of about 6 nM or less. In some embodiments, the compound has a K_i value of about 5 nM or less. In some embodiments, the compound has a K_i value of about 4 nM or less. In some embodiments, the compound has a K_i value of about 3 nM or less. In some embodiments, the compound has a K_i value of about 2 nM or less. In some embodiments, the compound has a K_i value of about 1 nM or less.

Some embodiments provide a compound, as described herein, or a pharmaceutically acceptable salt thereof, wherein the compound has a K_i value of about 50 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 25 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 20 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 15 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 10 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 9 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 8 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 7 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 6 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 5 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 4 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 3 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 2 nM to about 0.2 nM. In some embodiments, the compound has a K_i value of about 1 nM to about 0.2 nM.

Some embodiments provide a compound, as described herein, or a pharmaceutically acceptable salt thereof, wherein the compound has an elimination $t_{1/2} \geq 420$ minutes as determined using a human liver microsomes (HLM) assay, such as, the assay as described in **EXAMPLE 23**. In some embodiments, the compound has an elimination $t_{1/2} \geq 400$ minutes. In some embodiments, the compound has an elimination $t_{1/2} \geq 375$ minutes. In some embodiments, the compound has an elimination $t_{1/2} \geq 350$ minutes. In some embodiments, the compound has an elimination $t_{1/2} \geq 325$ minutes. In some embodiments, the compound has an elimination $t_{1/2} \geq 300$ minutes. In some embodiments, the compound has an elimination $t_{1/2} \geq 275$ minutes. In some embodiments, the compound has an elimination $t_{1/2} \geq 250$ minutes. In some embodiments, the compound has an elimination $t_{1/2} \geq 225$ minutes. In some embodiments, the compound has an elimination $t_{1/2} \geq 200$ minutes.

Some embodiments provide a compound, as described herein, or a pharmaceutically acceptable salt thereof, wherein the compound has an $IC_{50} > 6{,}000$ nM against CYP2D6 and CYP3A4, as determined using an IC_{50} method, such as, the method described in **EXAMPLE 24**. In some embodiments, the compound has an $IC_{50} > 6{,}000$ nM against CYP2D6. In some embodiments, the compound has an $IC_{50} > 5{,}000$ nM against CYP2D6. In some embodiments, the compound has an $IC_{50} > 4{,}000$ nM against CYP2D6. In some embodiments, the compound has an $IC_{50} > 3{,}000$ nM

against CYP2D6. In some embodiments, the compound has an IC_{50} > 2,000 nM against CYP2D6. In some embodiments, the compound has an IC_{50} > 6,000 nM against CYP3A4. In some embodiments, the compound has an IC_{50} > 5,000 nM against CYP3A4. In some embodiments, the compound has an IC_{50} > 4,000 nM against CYP3A4. In some embodiments, the compound has an IC_{50} > 3,000 nM against CYP3A4. In some embodiments, the compound has an IC_{50} > 2,000 nM against CYP3A4. In some embodiments, the compound is substantially inactive against CYP2D6. In some embodiments, the compound is substantially inactive against CYP3A4.

Some embodiments provide a compound, as described herein, or a pharmaceutically acceptable salt thereof, wherein the compound has an IC_{50} > 12,000 nM against hERG (human ether-a-go-go-related gene) as determined using an IC_{50} method, such as, the method described in **EXAMPLE 25**. In some embodiments, the compound has an IC_{50} > 11,000 nM against hERG. In some embodiments, the compound has an IC_{50} > 10,000 nM against hERG. In some embodiments, the compound has an IC_{50} > 9,000 nM against hERG. In some embodiments, the compound has an IC_{50} > 8,000 nM against hERG. In some embodiments, the compound has an IC_{50} > 7,000 nM against hERG. In some embodiments, the compound is substantially inactive against hERG.

The phrase "**compound as described herein**" or "compounds as described herein" refers to any compound or compounds in the present disclosure, *supra,* and *infra*. In some embodiments, the compound(s) is of Formula (**Ia**). In some embodiments, the compound(s) is of Formula (**Ic**). In some embodiments, the compound(s) is of Formula (**Ie**). In some embodiments, the compound(s) is of Formula (**Ig**). In some embodiments, the compound(s) is of Formula (**Ii**). In some embodiments, the compound(s) is of Formula (**Ik**). In some embodiments, the compound(s) is of Formula (**IIa**). In some embodiments, the compound(s) is of Formula (**IIc**). In some embodiments, the compound(s) is of Formula (**IIe**).

It is understood that the stereochemistry for the R^1 groups provided herein are assigned based on the R^1 group being bonded to the oxygen as shown in the formulae provided herein (*e.g.*, Formula (**Ia**), Formula (**Ic**), Formula (**Ie**), Formula (**Ig**), Formula (**Ii**), Formula (**Ik**), Formula (**IIa**), Formula (**IIc**), and Formula (**IIe**)).

In some embodiments, R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-

alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, and C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, and C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, CH_3-O-C_2-alkylene, C_1-C_5-alkyl, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, CH_3-O-C_2-alkylene, C_1-C_5-alkyl, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, CH_3-O-C_2-alkylene, C_1-C_5-alkyl, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-

cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, CH_3-O-C_2-alkylene, C_1-C_5-alkyl, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, oxolanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methylpropyl, oxetanyl, oxolanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, oxolanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl,

(oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methylpropyl, oxetanyl, oxolanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, oxolanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methylpropyl, oxetanyl, oxolanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1-cyclobutylethyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, oxolan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1-cyclobutylethyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-*d5*, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, oxolan-3-yl, pentyl, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1-cyclobutylethyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, oxolan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1-cyclobutylethyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-*d5*, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, oxolan-3-yl, pentyl, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl,

(3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 1-cyclobutylethyl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, oxolan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: ((1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 1-cyclobutylethyl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-

dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2,2-trifluoroethyl, 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 5,5,5-trifluoropentyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, oxolan-3-yl, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 1-cyclobutylethyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, oxolan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: ((1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl,

(3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 1-cyclobutylethyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2,2-trifluoroethyl, 2-cyclopropoxyethyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 5,5,5-trifluoropentyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, oxolan-3-yl, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-

hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*S*)-1-cyclobutylethyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (3*R*)-oxolan-3-yl, (3*S*)-oxolan-3-yl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 1,1,1-trifluoropropan-2-yl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*S*)-1-cyclobutylethyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3s)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 1,1,1-trifluoropropan-2-yl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-

difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3*R*)-oxolan-3-yl, (3*S*)-oxolan-3-yl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, 2,2,2-trifluoroethyl, 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 5,5,5-trifluoropentyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*S*)-1-cyclobutylethyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-

fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (3*R*)-oxolan-3-yl, (3*S*)-oxolan-3-yl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*S*)-1-cyclobutylethyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3s)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 1,1,1-trifluoropropan-2-yl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-

hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3*R*)-oxolan-3-yl, (3*S*)-oxolan-3-yl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, 2,2,2-trifluoroethyl, 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 5,5,5-trifluoropentyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, propan-2-yl, and propyl.

In some embodiments, R^1 is 3-7-membered-heterocyclyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is 4-5-membered-heterocyclyl.

In some embodiments, R^1 is selected from: oxetanyl and oxolanyl.

In some embodiments, R^1 is selected from: oxetan-3-yl and oxolan-3-yl.

In some embodiments, R^1 is 3-7-membered-heterocyclyl-C_1-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is (4-membered-heterocyclyl)CH_2 optionally substituted with one substituent selected from: halogen.

In some embodiments, R^1 is (oxetanyl)methyl optionally substituted with one substituent selected from: fluoro.

In some embodiments, R^1 is selected from: (oxetan-2-yl)methyl and (oxetan-3-yl)methyl, each optionally substituted with one substituent selected from: fluoro.

In some embodiments, R^1 is selected from: (3-fluorooxetan-3-yl)methyl, (oxetan-2-yl)methyl, and (oxetan-3-yl)methyl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (3-fluorooxetan-3-yl)methyl, and (oxetan-3-yl)methyl.

In some embodiments, R^1 is 4-8-membered-heterobicyclyl-C_1-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is (6-membered-heterobicyclyl)CH_2.

In some embodiments, R^1 is (oxabicyclo[2.1.1]hexanyl)methyl.

In some embodiments, R^1 is (2-oxabicyclo[2.1.1]hexan-4-yl)methyl.

In some embodiments, R^1 is C_1-C_4-alkyl-O-C_2-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is CH_3-O-C_2-alkylene optionally substituted with one, two, or three substituents selected from: halogen.

In some embodiments, R^1 is CH_3-O-C_2-alkylene optionally substituted with one, two, or three substituents selected from: fluoro.

In some embodiments, R^1 is (methoxy)ethyl optionally substituted with one, two, or three substituents selected from: fluoro.

In some embodiments, R^1 is selected from: 2-(trifluoromethoxy)ethyl and 2-methoxyethyl.

In some embodiments, R^1 is C_1-C_6-alkyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is C_1-C_5-alkyl optionally substituted with one, two, three, or four substituents selected from: halogen and hydroxyl.

In some embodiments, R^1 is selected from: butyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, pentyl, and propyl, wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: fluoro and hydroxyl.

In some embodiments, R^1 is selected from: 2,2-dimethylpropan-2-yl (neopentyl), 2-methylpropyl (isobutyl), butyl, ethyl, ethyl-d_5, methyl, methyl-d_3, pentyl, propan-2-yl (isopropyl), and propyl; wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: fluoro and hydroxyl.

In some embodiments, R^1 is selected from: 1,1,1-trifluoropropan-2-yl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: 1,1,1-trifluoropropan-2-yl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, 1,1,1-trifluoropropan-2-yl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, propan-2-yl, and propyl.

In some embodiments, R^1 is selected from: (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, 1,1,1-trifluoropropan-2-yl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, propan-2-yl, and propyl.

In some embodiments, R^1 is C_3-C_7-cycloalkyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is C_3-C_4-cycloalkyl optionally substituted with one or two substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, and halogen.

In some embodiments, R^1 is selected from: cyclobutyl and cyclopropyl; wherein each R^1 group is optionally substituted with one or two substituents selected from: fluoro, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: 3,3-dimethylcyclobutyl, 1-methylcyclobutyl, 3-(trifluoromethyl)cyclobutyl, 3,3-difluorocyclobutyl, 3-fluorocyclobutyl, 3-methoxycyclobutyl, cyclobutyl, and cyclopropyl.

In some embodiments, R^1 is selected from: 3,3-dimethylcyclobutyl, 3-(trifluoromethyl)cyclobutyl, 3,3-difluorocyclobutyl, 3-fluorocyclobutyl, 3-methoxycyclobutyl, cyclobutyl, and cyclopropyl.

In some embodiments, R^1 is selected from: (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, 1-methylcyclobutyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, cyclobutyl, and cyclopropyl.

In some embodiments, R^1 is selected from: (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, cyclobutyl, and cyclopropyl.

In some embodiments, R^1 is C_3-C_7-cycloalkyl-C_1-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is C_3-C_5-cycloalkyl-C_1-C_2-alkylene optionally substituted with one, two, or three substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, and cyclobutylmethyl; wherein each R^1 group is optionally substituted with one or two substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, and methyl.

In some embodiments, R^1 is selected from: 1-cyclobutylethyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, and 1-cyclobutylethyl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*S*)-1-cyclobutylethyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, [(1*R*)-

2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, and [(1*S*)-2,2-dimethylcyclopropyl]methyl.

In some embodiments, R^1 is C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is (cyclopropoxy)ethyl.

In some embodiments, R^1 is 2-cyclopropoxyethyl.

In some embodiments, R^1 is C_4-C_8-bicycloalkyl-C_1-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is (C_4-C_5-bicycloalkyl)CH_2.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl and (bicyclo[2.1.1]hexanyl)methyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentan-1-yl)methyl, and (bicyclo[2.1.1]hexan-1-yl)methyl.

In some embodiments, R^1 is C_5-C_{11}-spiro-cycloalkyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is C_7-spiro-cycloalkyl.

In some embodiments, R^1 is spiro[3.3]heptanyl.

In some embodiments, R^1 is spiro[3.3]heptan-2-yl.

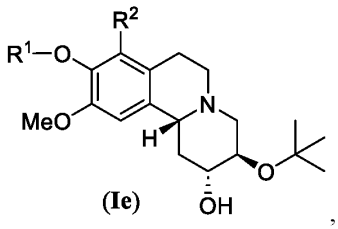
In some embodiments, R^1 is (1-(difluoromethyl)cyclopropyl)methyl. In some embodiments, R^1 is (1-cyanocyclobutyl)methyl. In some embodiments, R^1 is (1-cyanocyclopropyl)methyl. In some embodiments, R^1 is (1-fluorocyclobutyl)methyl. In some embodiments, R^1 is (1-fluorocyclopropyl)methyl. In some embodiments, R^1 is (1-hydroxycyclobutyl)methyl. In some embodiments, R^1 is (1-methylcyclobutyl)methyl. In some embodiments, R^1 is (1-methylcyclopropyl)methyl. In some embodiments, R^1 is (2,2-difluoro-3-methylcyclopropyl)methyl. In some embodiments, R^1 is (2,2-difluorocyclobutyl)methyl. In some embodiments, R^1 is (2,2-difluorocyclopentyl)methyl. In some embodiments, R^1 is (2,2-difluorocyclopropyl)methyl. In some embodiments, R^1 is (2,2-dimethylcyclopropyl)methyl. In some embodiments, R^1 is (2-fluorocyclopropyl)methyl. In some embodiments, R^1 is (2-oxabicyclo[2.1.1]hexan-4-yl)methyl. In some embodiments, R^1 is (3,3-difluorocyclobutyl)methyl. In some embodiments, R^1 is (3,3-difluorocyclopentyl)methyl. In some embodiments, R^1 is (3-fluorooxetan-3-yl)methyl. In some embodiments, R^1 is (bicyclo[1.1.1]pentan-1-yl)methyl. In some embodiments, R^1 is

(bicyclo[2.1.1]hexan-1-yl)methyl. In some embodiments, R^1 is (cyclobutyl)methyl. In some embodiments, R^1 is (cyclopropyl)methyl. In some embodiments, R^1 is (cyclopropyl)methyl-d_2. In some embodiments, R^1 is (oxetan-2-yl)methyl. In some embodiments, R^1 is (oxetan-3-yl)methyl. In some embodiments, R^1 is 1,1,1-trifluoropropan-2-yl. In some embodiments, R^1 is 1-cyclobutylethyl. In some embodiments, R^1 is 1-methylcyclobutyl. In some embodiments, R^1 is 2-(trifluoromethoxy)ethyl. In some embodiments, R^1 is 2,2,2-trifluoroethyl. In some embodiments, R^1 is 2,2-difluoroethyl. In some embodiments, R^1 is 2,2-difluoropropyl. In some embodiments, R^1 is 2,2-dimethylpropan-2-yl (neopentyl). In some embodiments, R^1 is 2-cyclopropoxyethyl. In some embodiments, R^1 is 2-fluoro-2-methylpropyl. In some embodiments, R^1 is 2-fluoroethyl. In some embodiments, R^1 is 2-fluoropropyl. In some embodiments, R^1 is 2-hydroxy-2-methylpropyl. In some embodiments, R^1 is 2-hydroxypropyl. In some embodiments, R^1 is 2-methoxyethyl. In some embodiments, R^1 is 2-methylpropyl (isobutyl). In some embodiments, R^1 is 3-(trifluoromethyl)cyclobutyl. In some embodiments, R^1 is 3,3,3-trifluoro-2-hydroxypropyl. In some embodiments, R^1 is 3,3,3-trifluoropropyl. In some embodiments, R^1 is 3,3-difluorocyclobutyl. In some embodiments, R^1 is 3,3-dimethylcyclobutyl. In some embodiments, R^1 is 3-fluorocyclobutyl. In some embodiments, R^1 is 3-fluoropropyl. In some embodiments, R^1 is 3-methoxycyclobutyl. In some embodiments, R^1 is 4,4,4-trifluorobutyl. In some embodiments, R^1 is 5,5,5-trifluoropentyl. In some embodiments, R^1 is butan-1-yl. In some embodiments, R^1 is cyclobutyl. In some embodiments, R^1 is cyclopropyl. In some embodiments, R^1 is ethyl. In some embodiments, R^1 is ethyl-d_5. In some embodiments, R^1 is fluoromethyl. In some embodiments, R^1 is methyl. In some embodiments, R^1 is methyl-d_3. In some embodiments, R^1 is oxetan-3-yl. In some embodiments, R^1 is oxolan-3-yl. In some embodiments, R^1 is propan-2-yl. In some embodiments, R^1 is propyl. In some embodiments, R^1 is spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is ((2*R*)-oxetan-2-yl)methyl. In some embodiments, R^1 is ((2*S*)-oxetan-2-yl)methyl. In some embodiments, R^1 is (1*R*)-1-cyclobutylethyl. In some embodiments, R^1 is (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl. In some embodiments, R^1 is (1*r*,3*r*)-3-fluorocyclobutyl. In some embodiments, R^1 is (1*r*,3*r*)-3-methoxycyclobutan-1-yl. In some embodiments, R^1 is (1*S*)-1-cyclobutylethyl. In some embodiments, R^1 is (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl. In some embodiments, R^1 is (1*s*,3*s*)-3-fluorocyclobutyl. In some embodiments, R^1 is (1*s*,3*s*)-3-methoxycyclobutan-1-yl. In some embodiments, R^1 is (2*R*)-2-fluoropropyl. In some embodiments, R^1 is (2*R*)-2-hydroxypropyl. In some embodiments, R^1 is (2*R*)-3,3,3-trifluoro-2-hydroxypropyl. In some embodiments, R^1 is (2*S*)-2-2-fluoropropyl. In some embodiments, R^1 is (2*S*)-2-hydroxypropyl. In some embodiments, R^1 is (2*S*)-3,3,3-trifluoro-2-hydroxypropyl. In some embodiments, R^1 is (3*R*)-oxolan-3-yl. In some embodiments, R^1 is (3*S*)-oxolan-3-yl. In some embodiments, R^1 is [(1*R*)-2,2-difluorocyclopropyl]methyl. In some embodiments, R^1 is [(1*S*)-2,2-difluorocyclopropyl]methyl. In some embodiments, R^1 is [(1*S*)-2,2-dimethylcyclopropyl]methyl. In some embodiments, R^1 is ((1*S*,2*S*)-2-fluorocyclopropyl)methyl. In some embodiments, R^1 is ((1*R*,2*R*)-2-

fluorocyclopropyl)methyl. In some embodiments, R^1 is ((1*R*,2*S*)-2-fluorocyclopropyl)methyl. In some embodiments, R^1 is ((1*S*,2*R*)-2-fluorocyclopropyl)methyl.

One aspect of the present disclosure encompasses, *inter alia*, a compound of (Ie):



(Ie) ,

or a pharmaceutically acceptable salt thereof,

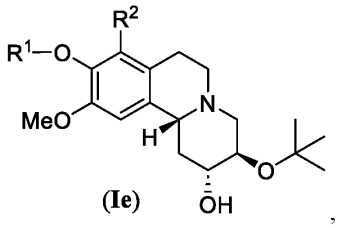
wherein:

R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl; and

R^2 is halogen.

One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula (Ie):



(Ie) ,

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl; and

R^2 is selected from: F, Cl, and Br.

In some embodiments, R^2 is F.

In some embodiments, R^2 is Cl.

In some embodiments, R^2 is Br.

In some embodiments, R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

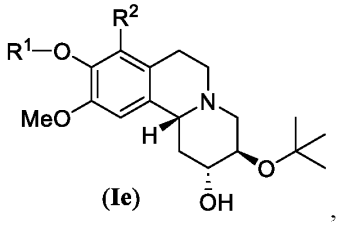
In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl,

butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1r,3r)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoroethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, propyl, and spiro[3.3]heptan-2-yl.

One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula (**Ie**):



(**Ie**),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, and C_3-C_7-cycloalkyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-haloalkyl, halogen, and hydroxyl; and

R^2 is selected from: F, Cl, and Br.

In some embodiments, R^2 is F.

In some embodiments, R^2 is Cl.

In some embodiments, R^2 is Br.

In some embodiments, R^1 is selected from: C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, and C_3-C_7-cycloalkyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-haloalkyl, halogen, and hydroxyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: difluoromethyl, fluoro, hydroxyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: difluoromethyl, fluoro, hydroxyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, 2-methoxyethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: difluoromethyl, fluoro, hydroxyl, and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, 2-methoxyethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: difluoromethyl, fluoro, hydroxyl, and trifluoromethyl.

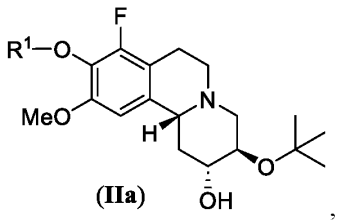
In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-fluorocyclopropyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2-fluoroethyl, 2-fluoropropyl, 2-methoxyethyl, 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, and propan-2-yl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-fluorocyclopropyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2*R*)-2-fluoropropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, [(1*S*)-2,2-difluorocyclopropyl]methyl, 2,2,2-

trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2-fluoroethyl, 2-methoxyethyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, and propan-2-yl.

In some embodiments, R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-fluorocyclopropyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2*R*)-2-fluoropropyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, [(1*S*)-2,2-difluorocyclopropyl]methyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2-fluoroethyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, cyclopropyl, ethyl, and ethyl-d_5.

One aspect of the present disclosure encompasses, *inter alia*, compounds of Formula (**IIa**):



(IIa),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: C_1-C_6-alkyl, C_3-C_7-cycloalkyl, and C_3-C_7-cycloalkyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-haloalkyl and halogen.

In some embodiments, R^1 is selected from: C_1-C_6-alkyl, C_3-C_7-cycloalkyl, and C_3-C_7-cycloalkyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one, two, or three substituents selected from: C_1-C_4-haloalkyl and halogen.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, cyclobutyl, cyclopropyl, ethyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: fluoro and trifluoromethyl.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, 2-methoxyethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: fluoro and trifluoromethyl.

In some embodiments, R^1 is selected from: (1-fluorocyclopropyl)methyl, (2,2-difluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl-d_2, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoropropyl, and cyclopropyl.

In some embodiments, R^1 is selected from: (1-fluorocyclopropyl)methyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl-d_2, [(1*S*)-2,2-difluorocyclopropyl]methyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, and cyclopropyl.

In some embodiments, R^1 is selected from C_1-C_6-alkyl optionally substituted with one, two, or three substituents selected from halogen.

In some embodiments, R^1 is selected from: ethyl and propyl; wherein each R^1 group is optionally substituted with one, two, or three substituents selected from fluoro.

In some embodiments, R^1 is selected from: 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, and 3,3,3-trifluoropropyl.

In some embodiments, R^1 is selected from C_3-C_7-cycloalkyl optionally substituted with one substituent selected from C_1-C_4-haloalkyl.

In some embodiments, R^1 is selected from: cyclobutyl and cyclopropyl; wherein each R^1 group is optionally substituted with one substituent selected from trifluoromethyl.

In some embodiments, R^1 is selected from: cyclopropyl and 3-(trifluoromethyl)cyclobutyl.

In some embodiments, R^1 is selected from: cyclopropyl and (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl.

In some embodiments, R^1 is selected from: C_3-C_7-cycloalkyl-C_1-C_4-alkylene optionally substituted with one or two, substituents selected from halogen.

In some embodiments, R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, and (cyclopropyl)methyl-d_2; wherein each R^1 group is optionally substituted with one or two substituents selected from fluoro.

In some embodiments, R^1 is selected from: (1-fluorocyclopropyl)methyl, (2,2-difluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, and (cyclopropyl)methyl-d_2.

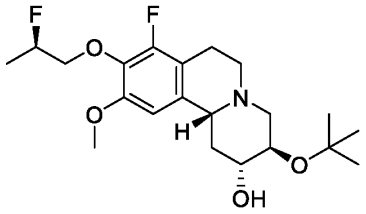
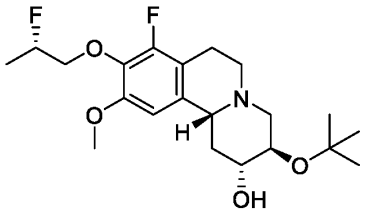
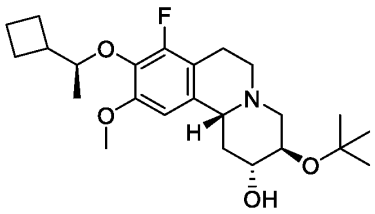
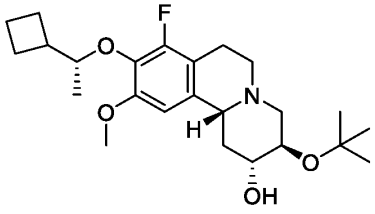
In some embodiments, R^1 is selected from: (1-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, and [(1*S*)-2,2-difluorocyclopropyl]methyl.

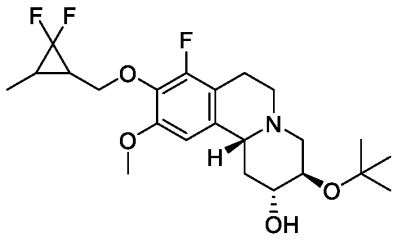
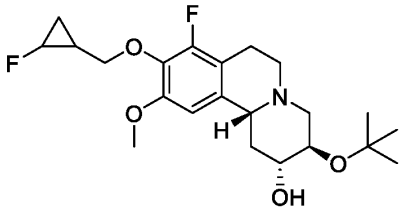
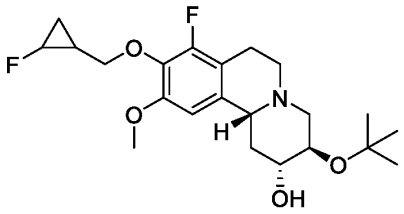
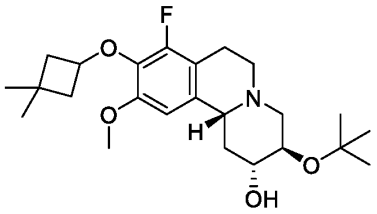
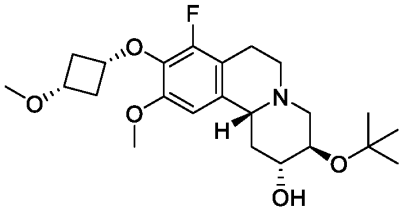
Some embodiments include every combination of one or more compounds and pharmaceutically acceptable salts thereof selected from the following group of compounds shown in **Table A**, **Table B**, **Table C**, and **Table D**.

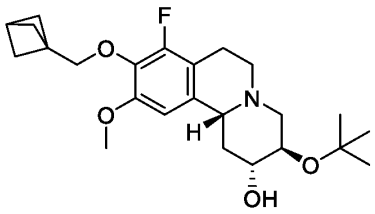
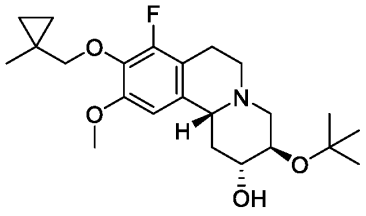
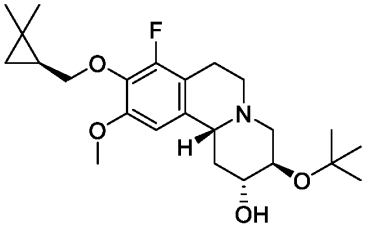
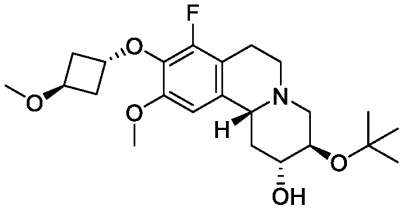
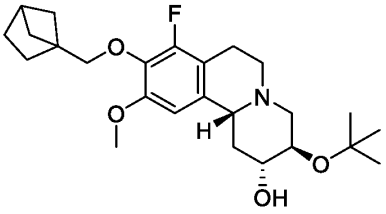
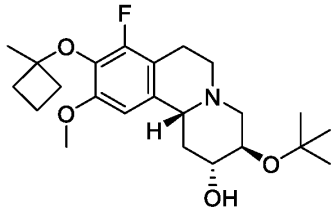
Some embodiments include every combination of one or more compounds and pharmaceutically acceptable salts thereof selected from the following group of compounds shown in **Table A**, **Table B**, and **Table C**.

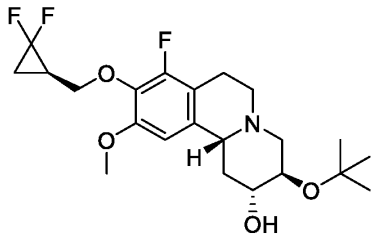
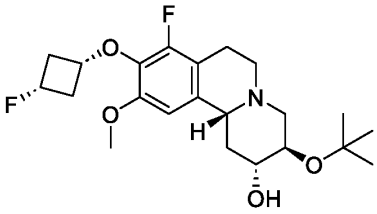
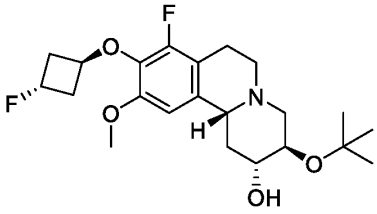
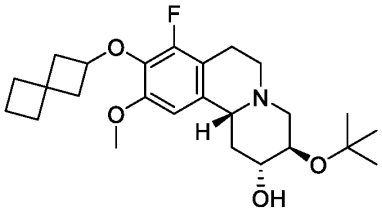
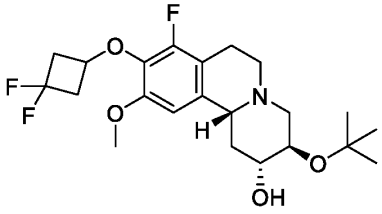
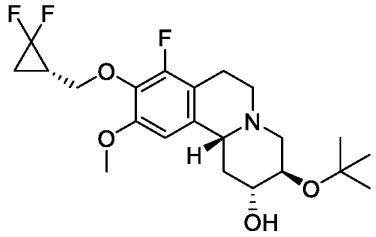
Some embodiments include every combination of one or more compounds selected from the following group shown in **Table A**.

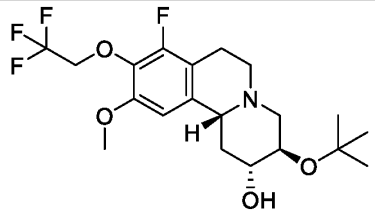
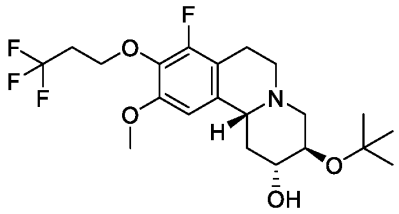
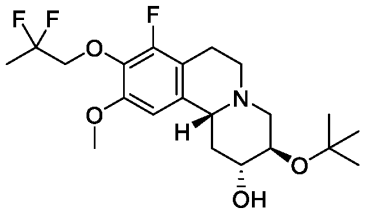
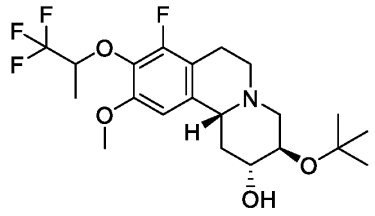
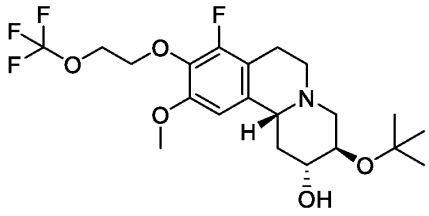
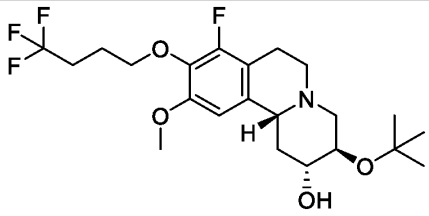
Table A

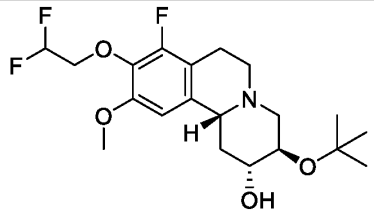
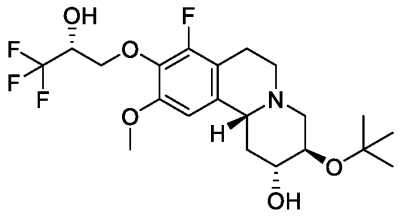
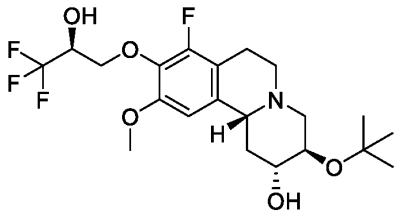
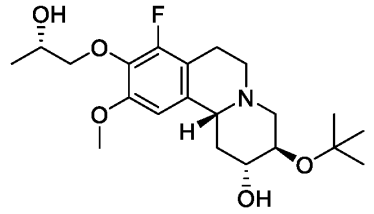
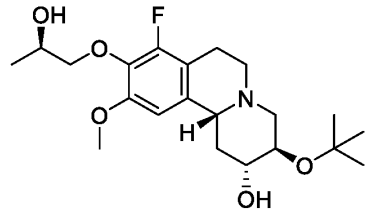
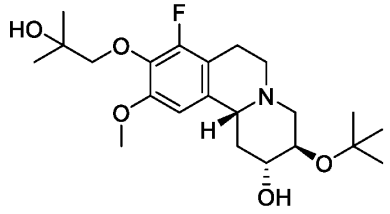
Cmpd No.	Chemical Structure	Chemical Name
1		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*R*)-2-fluoropropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
2		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*S*)-2-fluoropropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
3		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(1*S*)-1-cyclobutylethoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
4		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(1*R*)-1-cyclobutylethoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

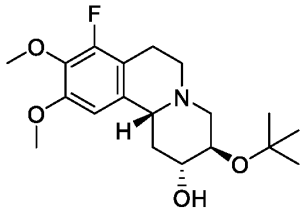
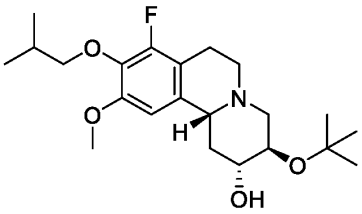
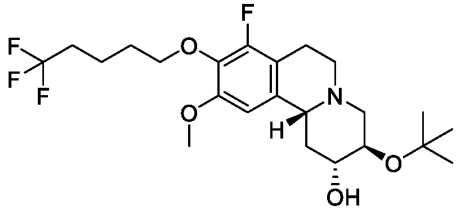
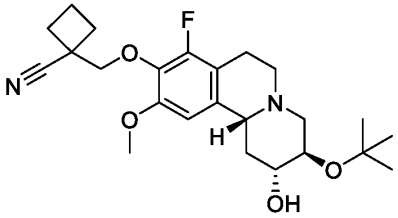
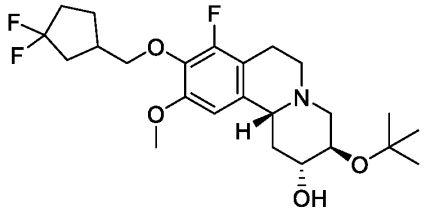
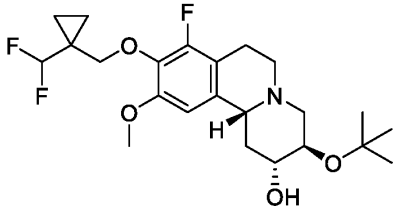
Cmpd No.	Chemical Structure	Chemical Name
5[1]		*trans*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluoro-3-methylcyclopropyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
6[2]		*cis*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
7[1]		*trans*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
8		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(3,3-dimethylcyclobutoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
9		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-methoxycyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

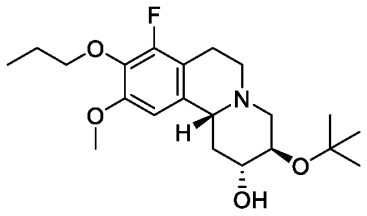
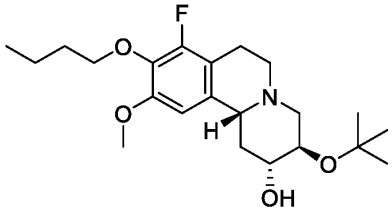
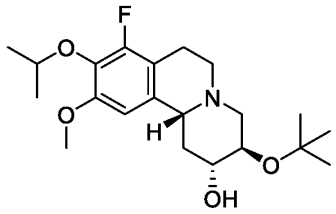
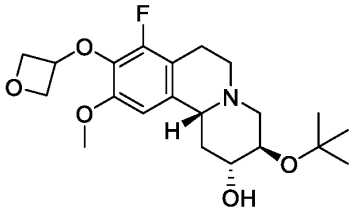
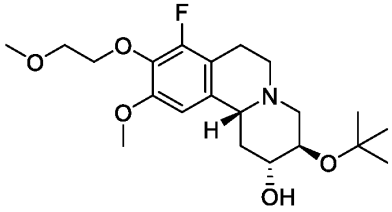
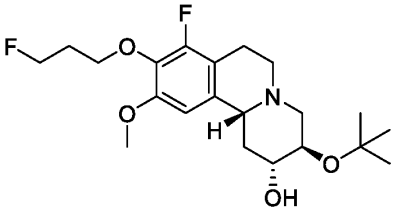
Cmpd No.	Chemical Structure	Chemical Name
10		(2*R*,3*R*,11b*R*)-9-{bicyclo[1.1.1]pentan-1-ylmethoxy}-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
11		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1-methylcyclopropyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
12		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-dimethylcyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
13		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-methoxycyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
14		(2*R*,3*R*,11b*R*)-9-{bicyclo[2.1.1]hexan-1-ylmethoxy}-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
15		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(1-methylcyclobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

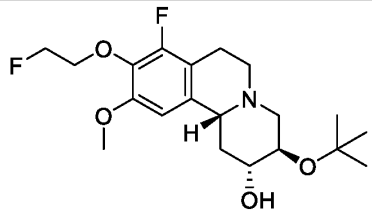
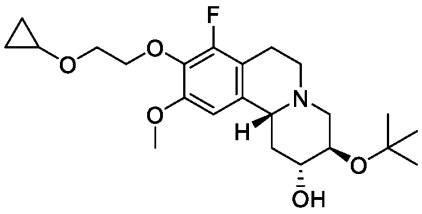
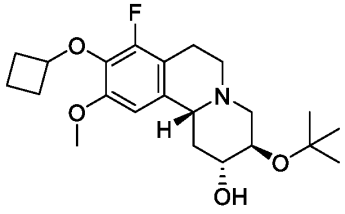
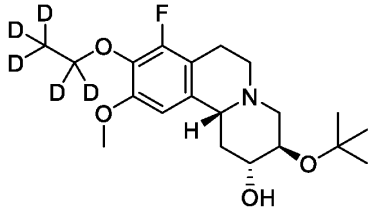
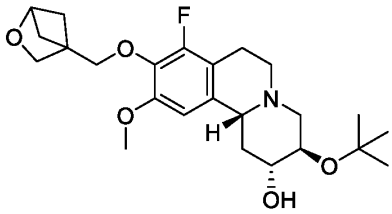
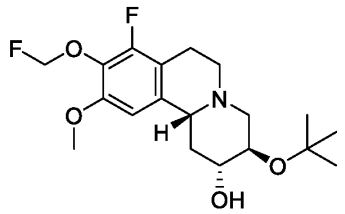
Cmpd No.	Chemical Structure	Chemical Name
16		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*R*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
17		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-fluorocyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
18		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-fluorocyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
19		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-{spiro[3.3]heptan-2-yloxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
20		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(3,3-difluorocyclobutoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
21		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

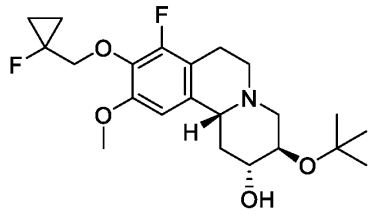
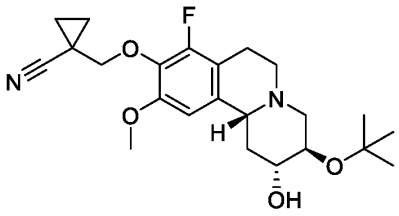
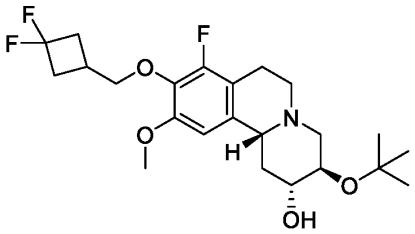
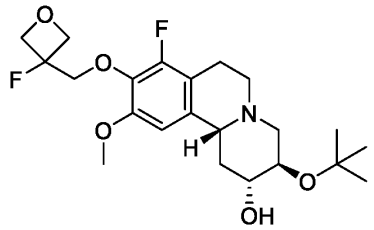
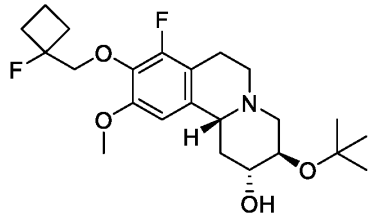
Cmpd No.	Chemical Structure	Chemical Name
22		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
23		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
24		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
25		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1,1,1-trifluoropropan-2-yl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
26		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[2-(trifluoromethoxy)ethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
27		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(4,4,4-trifluorobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

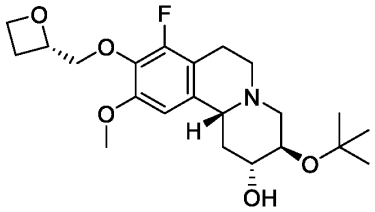
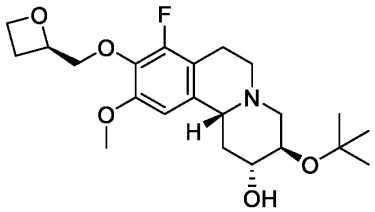
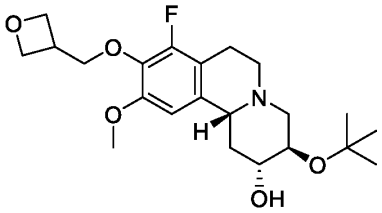
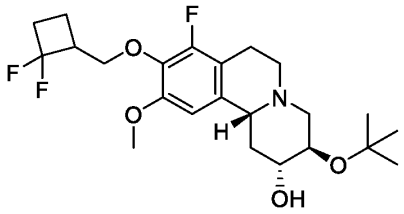
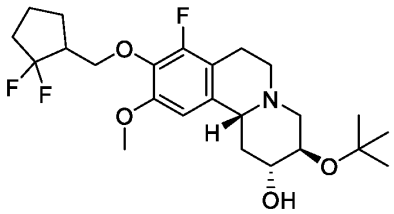
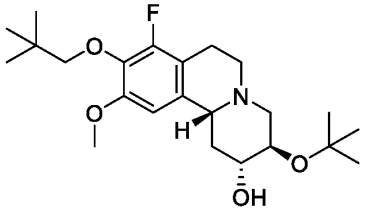
Cmpd No.	Chemical Structure	Chemical Name
28		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
29		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
30		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
31		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
32		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
33		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-hydroxy-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

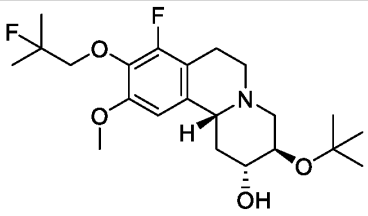
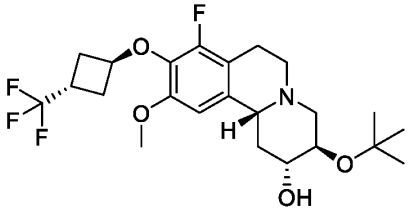
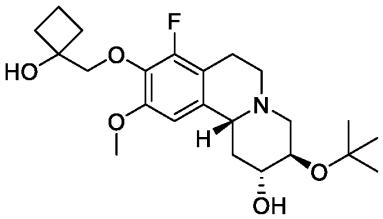
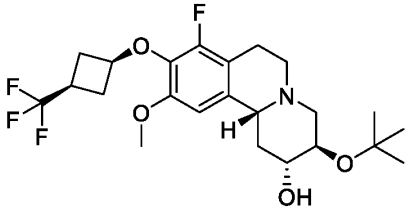
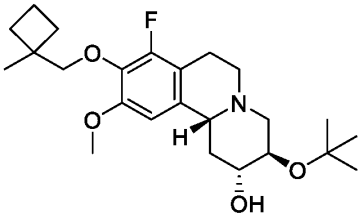
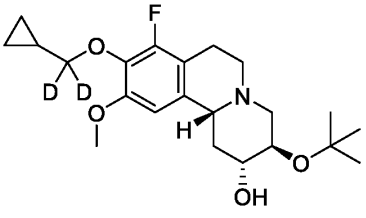
Cmpd No.	Chemical Structure	Chemical Name
34		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
35		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
36		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
37		1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile
38		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclopentyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
39		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

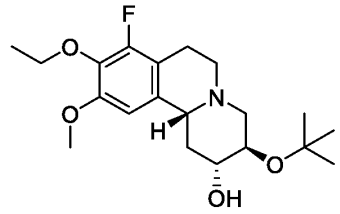
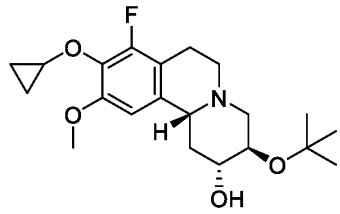
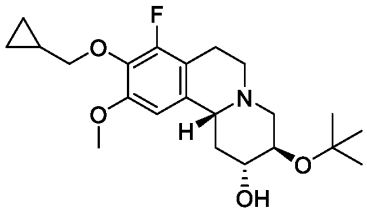
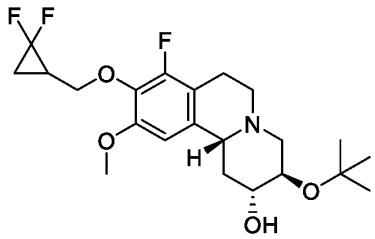
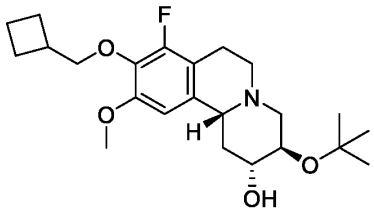
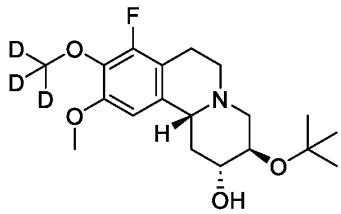
Cmpd No.	Chemical Structure	Chemical Name
40		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
41		(2*R*,3*R*,11b*R*)-9-butoxy-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
42		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
43		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
44		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
45		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(3-fluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
46		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-fluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
47		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2-cyclopropoxyethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
48		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclobutoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
49		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-($^{2}H_{5}$)ethoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
50		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-{2-oxabicyclo[2.1.1]hexan-4-ylmethoxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
51		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(fluoromethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
52		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
53		1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclopropane-1-carbonitrile
54		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
55		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(3-fluorooxetan-3-yl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
56		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
57		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
58		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
59		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
60		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
61		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopentyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
62		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-dimethylpropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
63		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
64		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
65		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
66		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
67		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
68		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

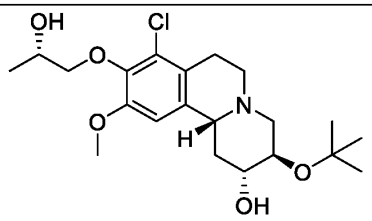
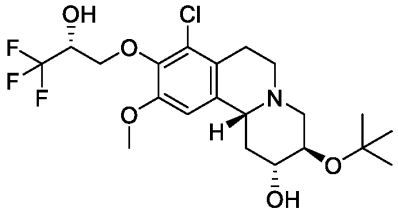
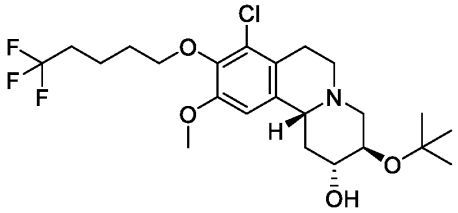
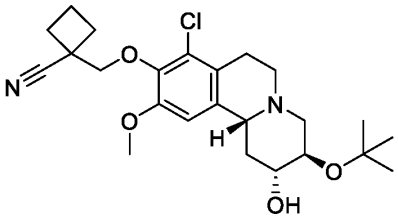
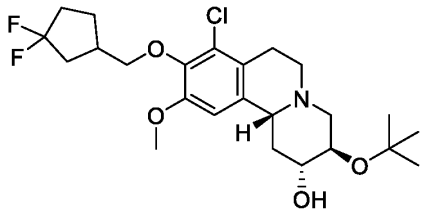
Cmpd No.	Chemical Structure	Chemical Name
69		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-ethoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
70		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclopropoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
71		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(cyclopropylmethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
72		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopropyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
73		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(cyclobutylmethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
74		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-($^{2}H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

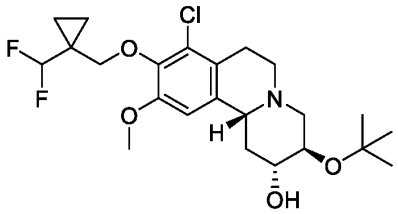
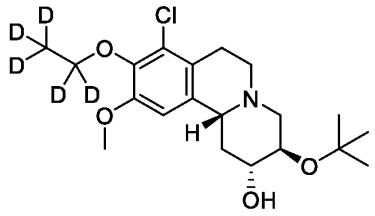
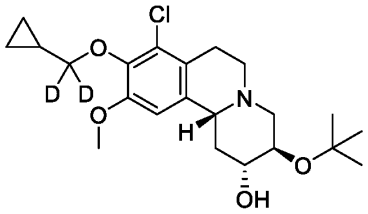
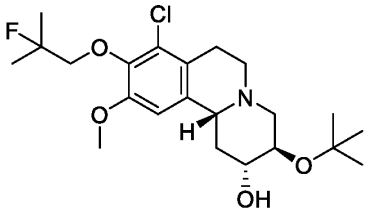
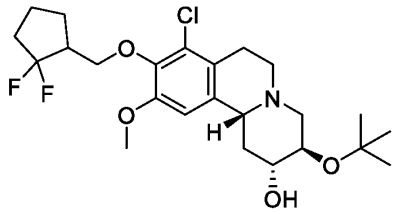
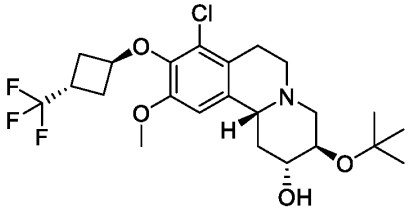
[1] Mixture of *trans* isomers (cyclopropyl).

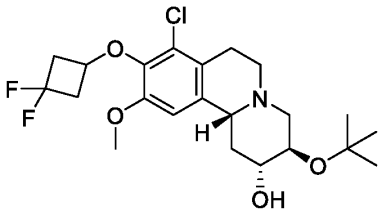
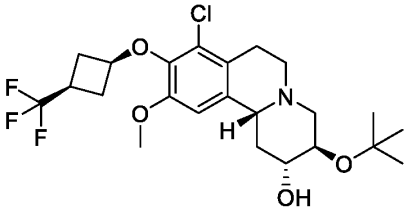
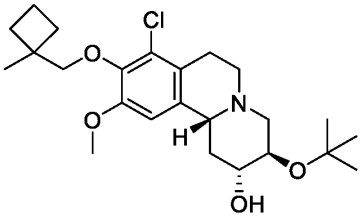
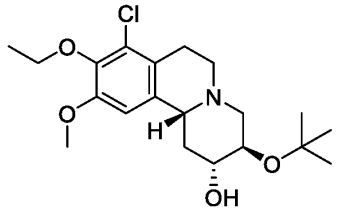
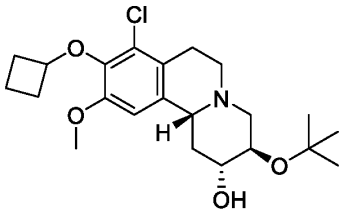
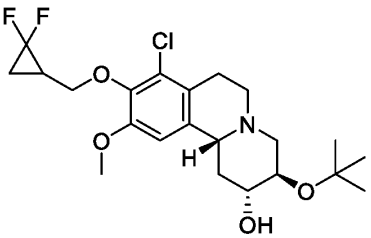
[2] Mixture of *cis* isomers (cyclopropyl).

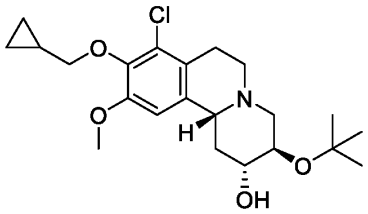
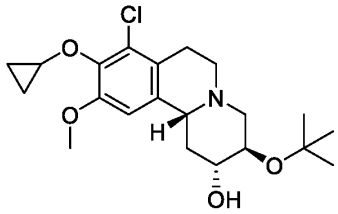
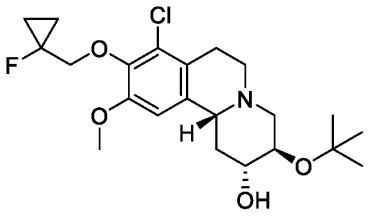
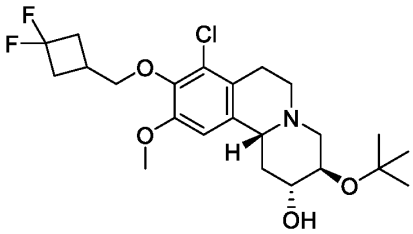
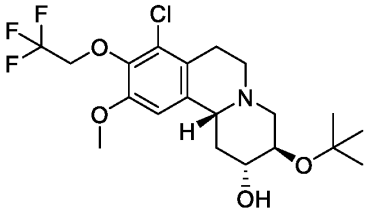
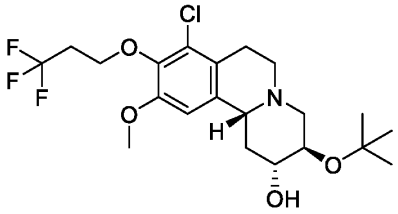
Some embodiments include every combination of one or more compounds selected from the following group shown in **Table B**.

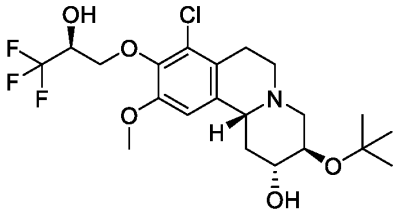
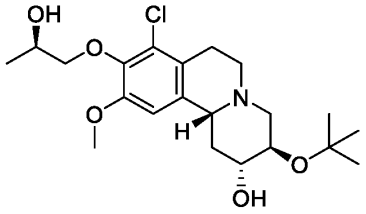
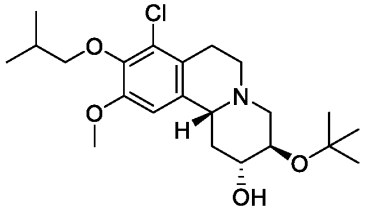
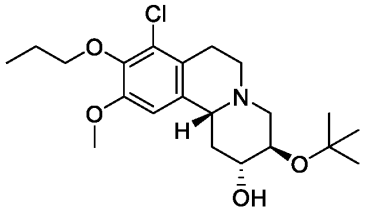
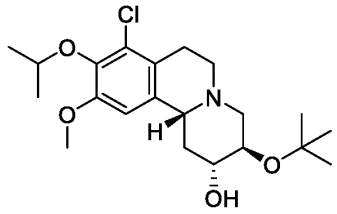
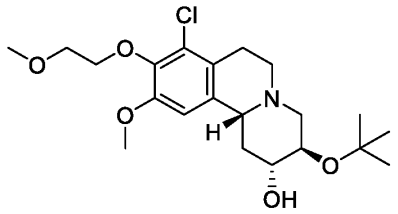
Table B

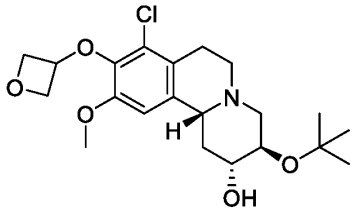
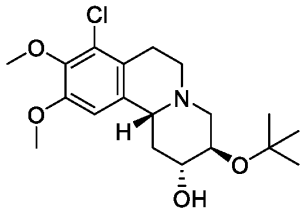
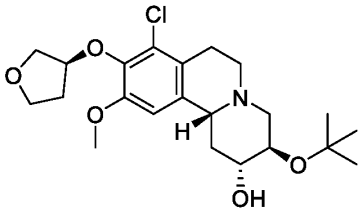
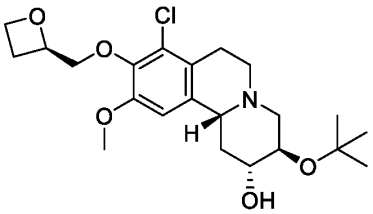
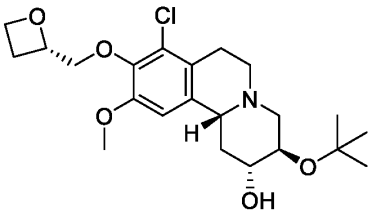
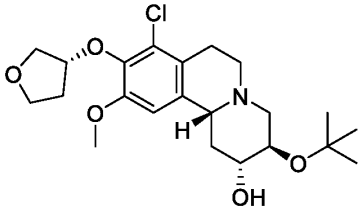
Cmpd No.	Chemical Structure	Chemical Name
75		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
76		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
77		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
78		1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile
79		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(3,3-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

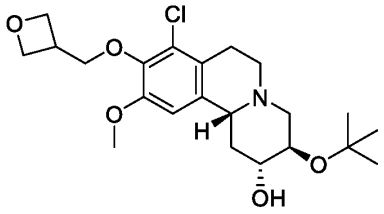
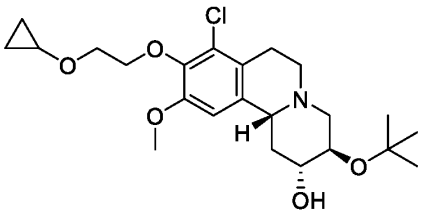
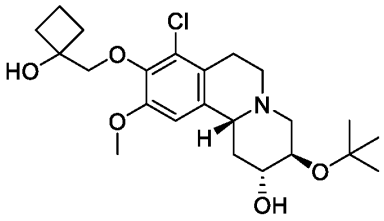
Cmpd No.	Chemical Structure	Chemical Name
80		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
81		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-($^{2}H_5$)ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
82		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[cyclopropyl($^{2}H_2$)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
83		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
84		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2,2-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
85		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
86		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(3,3-difluorocyclobutoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
87		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
88		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
89		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
90		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-cyclobutoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
91		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2,2-difluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
92		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(cyclopropylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
93		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-cyclopropoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
94		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
95		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(3,3-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
96		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
97		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

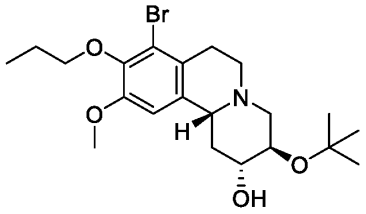
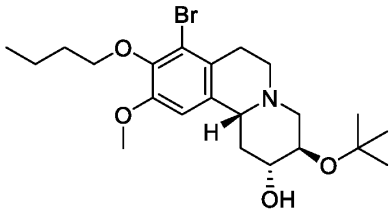
Cmpd No.	Chemical Structure	Chemical Name
98		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
99		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
100		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
101		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
102		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
103		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

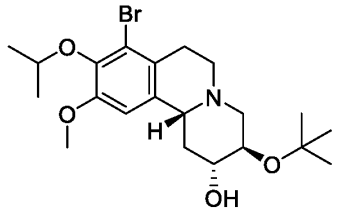
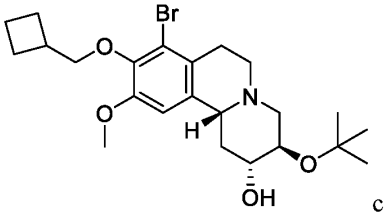
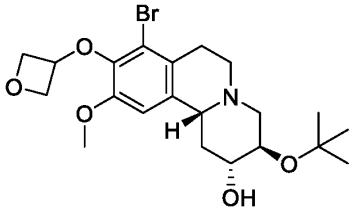
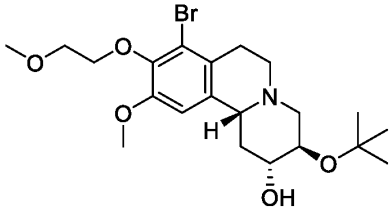
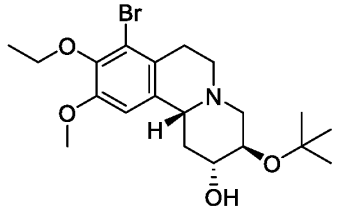
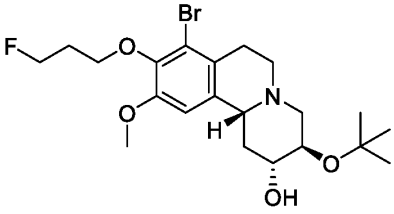
Cmpd No.	Chemical Structure	Chemical Name
104		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
105		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
106		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(3*S*)-oxolan-3-yloxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
107		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
108		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
109		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(3*R*)-oxolan-3-yloxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

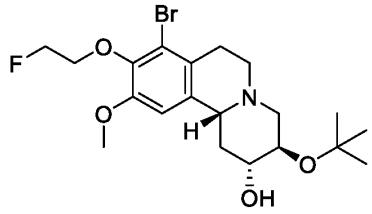
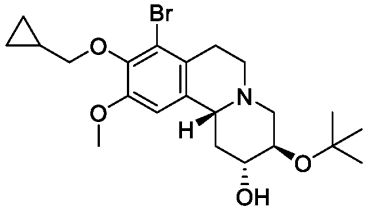
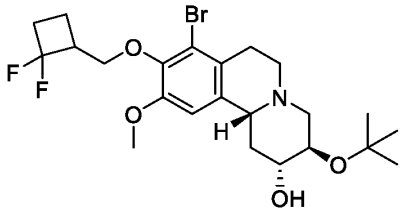
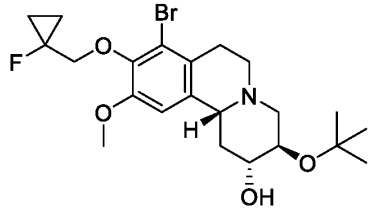
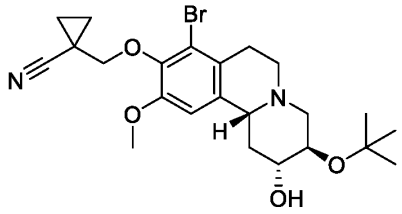
Cmpd No.	Chemical Structure	Chemical Name
110		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
111		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(2-cyclopropoxyethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
112		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

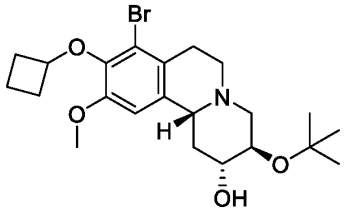
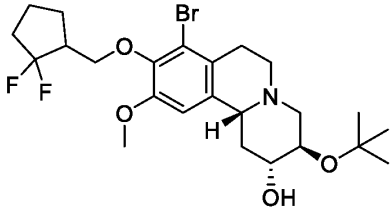
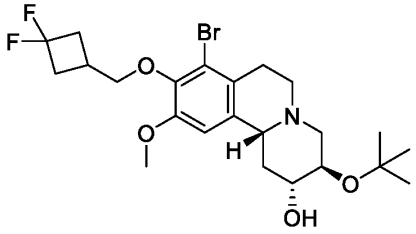
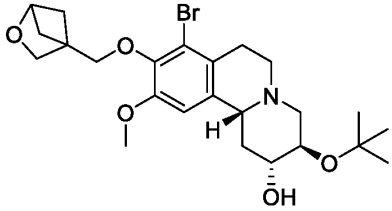
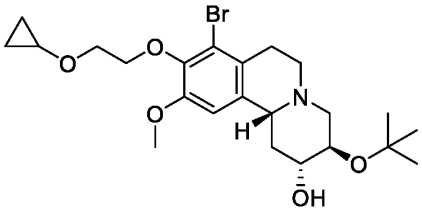
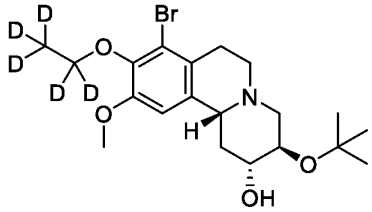
Some embodiments include every combination of one or more compounds selected from the following group shown in **Table C**.

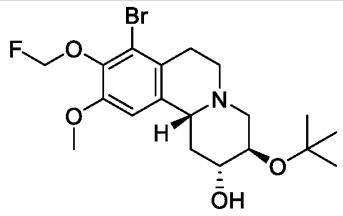
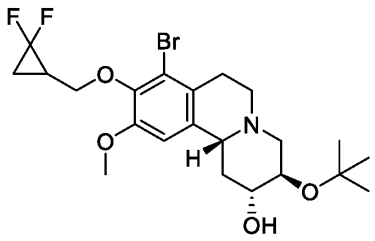
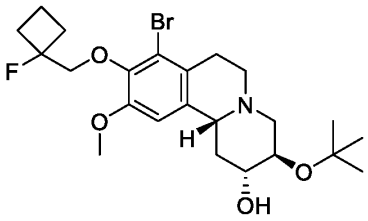
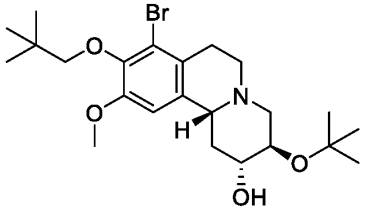
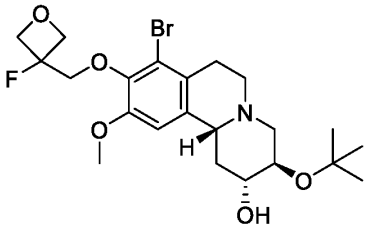
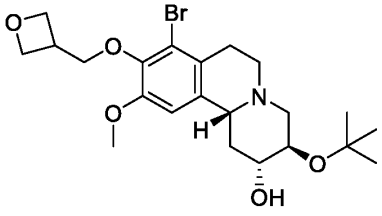
Table C

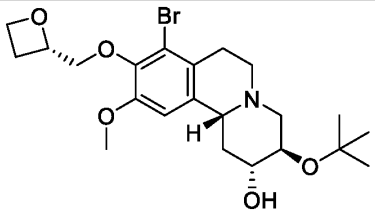
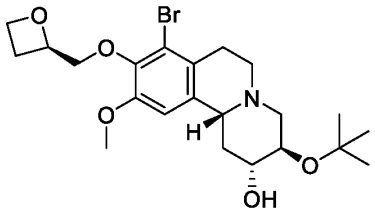
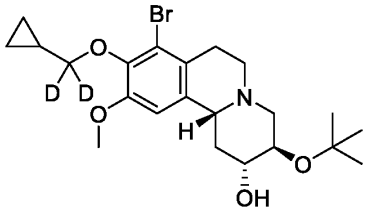
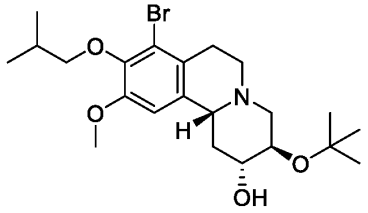
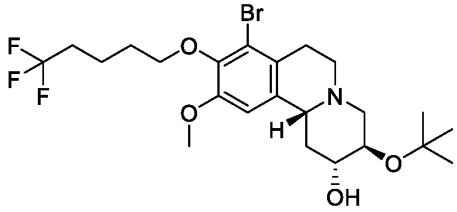
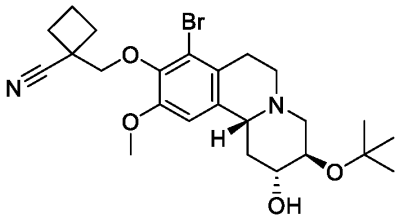
Cmpd No.	Chemical Structure	Chemical Name
113		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
114		(2*R*,3*R*,11b*R*)-8-bromo-9-butoxy-3-(*tert*-butoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

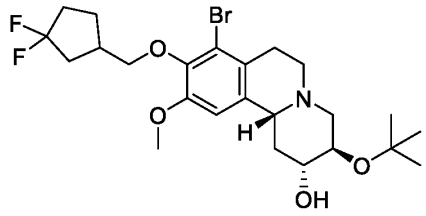
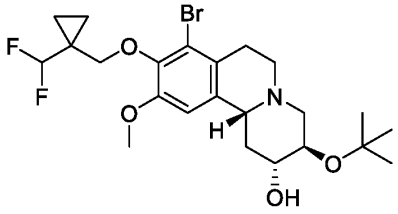
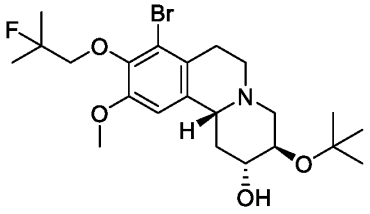
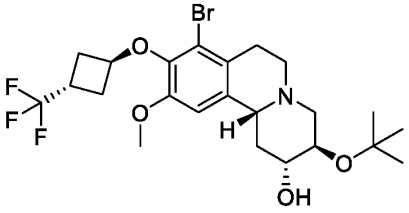
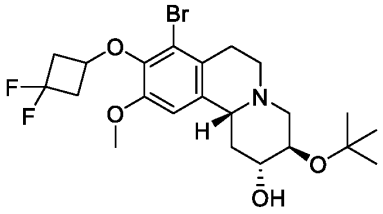
Cmpd No.	Chemical Structure	Chemical Name
115		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
116		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(cyclobutylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
117		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
118		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
119		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
120		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(3-fluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

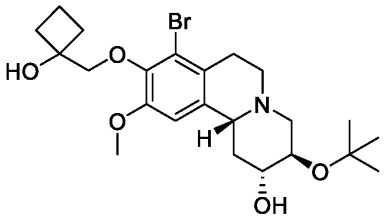
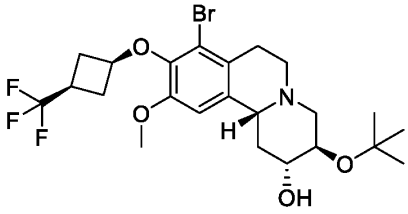
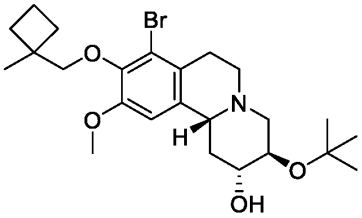
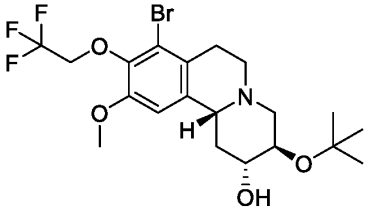
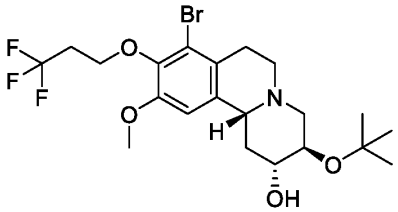
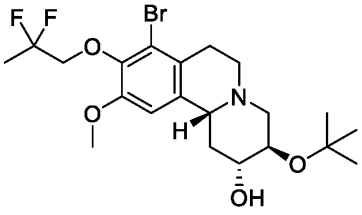
Cmpd No.	Chemical Structure	Chemical Name
121		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-fluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
122		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(cyclopropylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
123		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
124		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
125		1-({[(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclopropane-1-carbonitrile

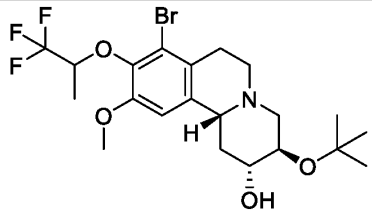
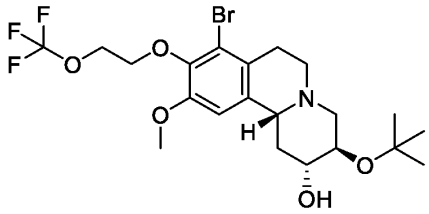
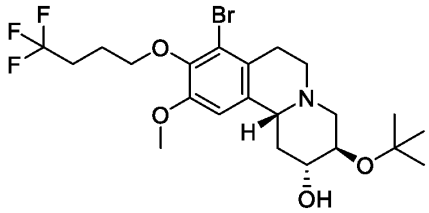
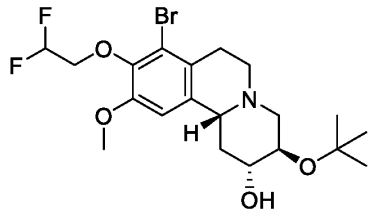
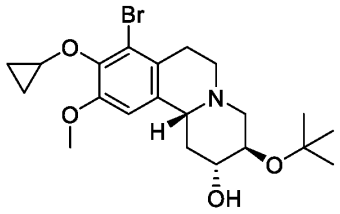
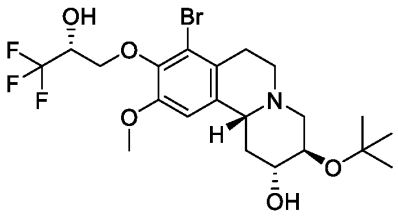
Cmpd No.	Chemical Structure	Chemical Name
126		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-cyclobutoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
127		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
128		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
129		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-{2-oxabicyclo[2.1.1]hexan-4-ylmethoxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
130		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-cyclopropoxyethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
131		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^{2}H_5$)ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

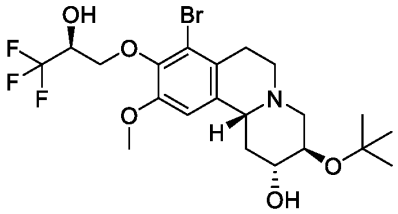
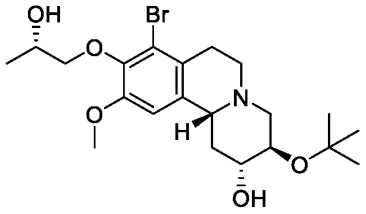
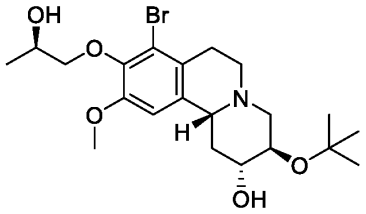
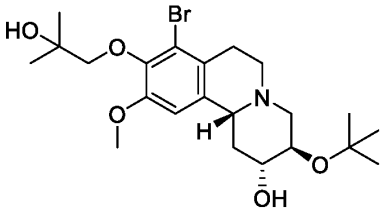
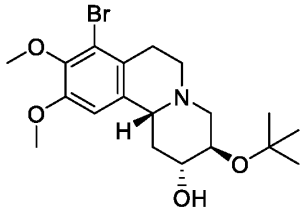
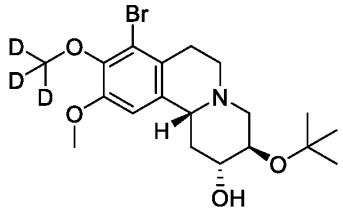
Cmpd No.	Chemical Structure	Chemical Name
132		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(fluoromethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
133		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
134		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-fluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
135		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-dimethylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
136		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3-fluorooxetan-3-yl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
137		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
138		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
139		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
140		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
141		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
142		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
143		1-({[(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile

Cmpd No.	Chemical Structure	Chemical Name
144		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3,3-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
145		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
146		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
147		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
148		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(3,3-difluorocyclobutoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

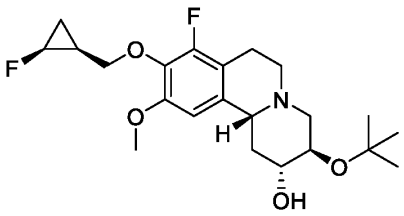
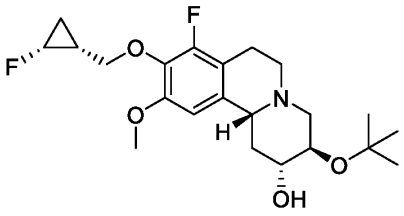
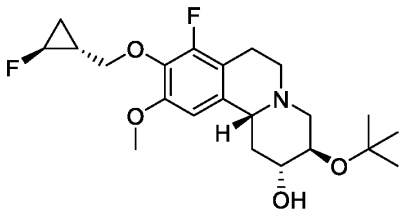
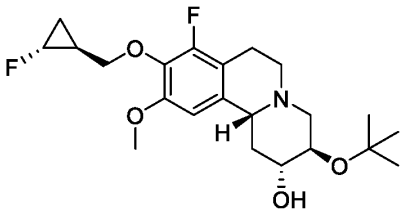
Cmpd No.	Chemical Structure	Chemical Name
149		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
150		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
151		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
152		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
153		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
154		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
155		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1,1,1-trifluoropropan-2-yl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
156		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[2-(trifluoromethoxy)ethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
157		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(4,4,4-trifluorobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
158		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
159		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-cyclopropoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
160		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Cmpd No.	Chemical Structure	Chemical Name
161		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
162		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
163		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
164		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-hydroxy-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
165		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
166		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^{2}H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Some embodiments include every combination of one or more compounds selected from the following group shown in **Table D**.

Table D

Cmpd No.	Chemical Structure	Chemical Name
167		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*S*,2*S*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
168		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*R*,2*R*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
169		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*R*,2*S*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol
170		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*S*,2*R*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol

Some embodiments of the present invention include every combination of one or more compounds selected from the following group: (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*R*)-2-fluoropropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 1**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*S*)-2-fluoropropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 2**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(1*S*)-1-cyclobutylethoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 3**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(1*R*)-1-cyclobutylethoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 4**); *trans*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluoro-3-methylcyclopropyl)methoxy]-8-fluoro-10-methoxy-

1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 5**); *cis*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 6**); *trans*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 7**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(3,3-dimethylcyclobutoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 8**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-methoxycyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 9**); (2*R*,3*R*,11b*R*)-9-{bicyclo[1.1.1]pentan-1-ylmethoxy}-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 10**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1-methylcyclopropyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 11**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-dimethylcyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 12**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-methoxycyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 13**); (2*R*,3*R*,11b*R*)-9-{bicyclo[2.1.1]hexan-1-ylmethoxy}-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 14**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(1-methylcyclobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 15**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*R*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 16**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-fluorocyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 17**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-fluorocyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 18**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-{spiro[3.3]heptan-2-yloxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 19**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(3,3-difluorocyclobutoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 20**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 21**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 22**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 23**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 24**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1,1,1-trifluoropropan-2-yl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 25**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[2-(trifluoromethoxy)ethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 26**); (2*R*,3*R*,11b*R*)-3-(*tert*-

butoxy)-8-fluoro-10-methoxy-9-(4,4,4-trifluorobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 27**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 28**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 29**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 30**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 31**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 32**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-hydroxy-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 33**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 34**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 35**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 36**); 1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile (**Compound 37**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclopentyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 38**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 39**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 40**); (2*R*,3*R*,11b*R*)-9-butoxy-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 41**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 42**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 43**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 44**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(3-fluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 45**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-fluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 46**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2-cyclopropoxyethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 47**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclobutoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 48**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-($^{2}H_5$)ethoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 49**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-{2-oxabicyclo[2.1.1]hexan-4-ylmethoxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 50**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(fluoromethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 51**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 52**); 1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclopropane-1-carbonitrile (**Compound 53**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 54**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(3-fluorooxetan-3-yl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 55**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 56**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 57**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 58**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 59**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 60**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopentyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 61**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-dimethylpropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 62**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 63**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 64**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 65**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 66**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 67**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 68**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-ethoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 69**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclopropoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 70**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(cyclopropylmethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 71**); (2*R*,3*R*,11b*R*)-3-(*tert*-

butoxy)-9-[(2,2-difluorocyclopropyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 72**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(cyclobutylmethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 73**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-($^{2}H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 74**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 75**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 76**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 77**); 1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile (**Compound 78**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(3,3-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 79**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 80**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-($^{2}H_5$)ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 81**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[cyclopropyl($^{2}H_2$)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 82**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 83**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2,2-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 84**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 85**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(3,3-difluorocyclobutoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 86**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 87**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 88**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 89**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-cyclobutoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 90**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2,2-difluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 91**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(cyclopropylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 92**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-cyclopropoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 93**); (2*R*,3*R*,11b*R*)-3-(*tert*-

butoxy)-8-chloro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 94**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(3,3-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 95**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 96**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 97**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 98**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 99**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 100**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 101**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 102**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 103**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 104**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 105**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(3*S*)-oxolan-3-yloxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 106**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 107**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 108**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(3*R*)-oxolan-3-yloxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 109**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 110**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(2-cyclopropoxyethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 111**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 112**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 113**); (2*R*,3*R*,11b*R*)-8-bromo-9-butoxy-3-(*tert*-butoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 114**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 115**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(cyclobutylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 116**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 117**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 118**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 119**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(3-fluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 120**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-fluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 121**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(cyclopropylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 122**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 123**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 124**); 1-({[(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclopropane-1-carbonitrile (**Compound 125**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-cyclobutoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 126**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 127**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 128**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-{2-oxabicyclo[2.1.1]hexan-4-ylmethoxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 129**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-cyclopropoxyethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 130**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^2H_5$)ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 131**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(fluoromethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 132**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 133**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-fluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 134**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-dimethylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 135**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3-fluorooxetan-3-yl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 136**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 137**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 138**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*R*)-

oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 139**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 140**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 141**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 142**); 1-({[(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile (**Compound 143**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3,3-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 144**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 145**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 146**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 147**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(3,3-difluorocyclobutoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 148**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 149**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 150**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 151**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 152**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 153**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 154**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1,1,1-trifluoropropan-2-yl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 155**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[2-(trifluoromethoxy)ethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 156**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(4,4,4-trifluorobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 157**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 158**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-cyclopropoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 159**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 160**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 161**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 162**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 163**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-hydroxy-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 164**); (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 165**); and (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^2H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 166**); or a pharmaceutically acceptable salt thereof.

Some embodiments of the present invention include every combination of one or more compounds selected from the following group: (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*S*,2*S*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 167**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*R*,2*R*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 168**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*R*,2*S*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 169**); and (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*S*,2*R*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 170**); or a pharmaceutically acceptable salt thereof.

Some embodiments of the present invention include every combination of one or more compounds selected from the following group: (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 21**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 22**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 23**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 24**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 28**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 52**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 54**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 66**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-8-fluoro-10-methoxy-

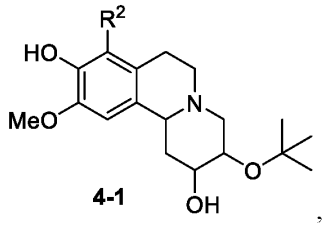
1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 68**); and (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclopropoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 70**); or a pharmaceutically acceptable salt thereof.

Some embodiments of the present invention include every combination of one or more compounds selected from the following group: (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 21**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 22**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 23**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 24**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 28**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 52**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 54**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 66**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 68**); and (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclopropoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 70**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*S*,2*S*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 167**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*R*,2*R*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 168**); (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*R*,2*S*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 169**); and (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[((1*S*,2*R*)-2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 170**); or a pharmaceutically acceptable salt thereof.

USEFUL INTERMEDIATES

Certain intermediates as described herein, *supra,* and *infra*, are novel and useful in the preparation of compounds, such as, compounds of Formula (**Ia**), Formula (**Ic**), Formula (**Ie**), Formula (**Ig**), Formula (**Ii**), Formula (**Ik**), Formula (**IIa**), Formula (**IIc**), and Formula (**IIe**). Certain intermediates are shown in **FIG. 3**, **FIG. 4**, **FIG. 5**, **FIG. 6**, **FIG. 7**, and **FIG. 8**.

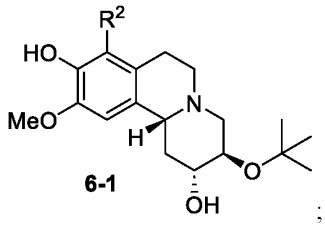
One aspect of the present disclosure is a compound of Formula (**4-1**):



4-1,

or a salt thereof, wherein R^2 is halogen.

In some embodiments, the compound is of the Formula (**6-1**):



6-1;

or a salt thereof, wherein R^2 is halogen.

In some embodiments, R^2 is selected from: F, Cl, and Br.

In some embodiments, the compound of Formula (**4-1**) is selected from:

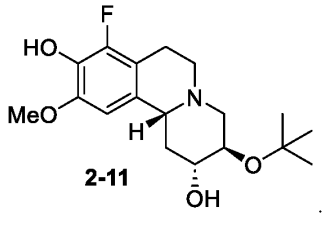
(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 2-11**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 3-1**); and

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 3-2**);

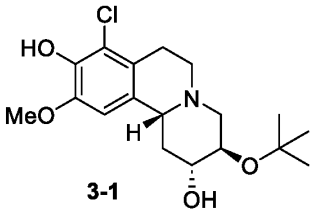
or a salt thereof.

In some embodiments, the compound is (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 2-11**), or a salt thereof;



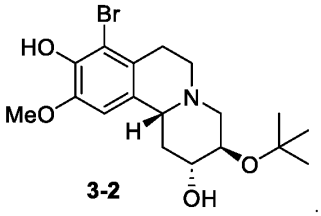
2-11.

In some embodiments, the compound is (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 3-1**), or a salt thereof;



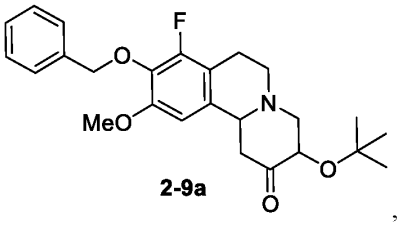
3-1

In some embodiments, the compound is (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 3-2**), or a salt thereof;



3-2

One aspect of the present disclosure is a compound of Formula (**2-9a**):



2-9a

or a salt thereof.

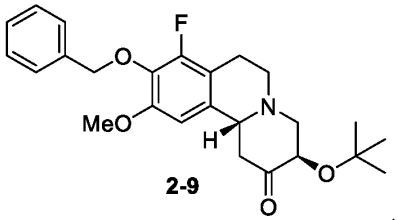
In some embodiments, the compound of Formula (**2-9a**) is selected from:

(3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9**); and

(3*S*,11b*S*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9c**);

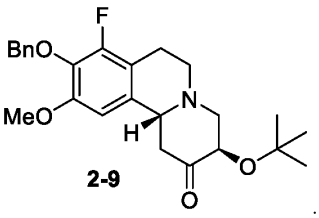
or a salt thereof.

In some embodiments, the compound is (3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9**), or a salt thereof;



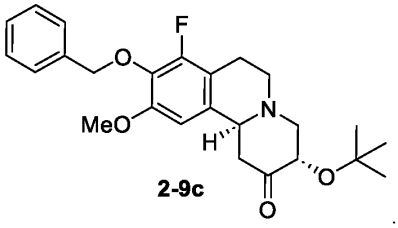
2-9

Alternatively, it is understood that the compound is (3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9**), or a salt thereof, can also be represented as the following chemical structure:



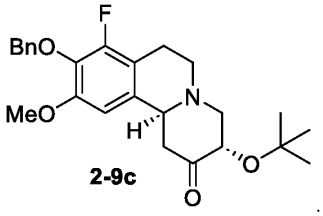
2-9

In some embodiments, the compound is (3*S*,11b*S*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9c**), or a salt thereof;



2-9c

Alternatively, it is understood that the compound is (3*S*,11b*S*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9c**), or a salt thereof, can also be represented as the following chemical structure:



2-9c

One aspect of the present disclosure relates to a composition comprising:

(3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9**); and

(3*S*,11b*S*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-one (**Compound 2-9c**);

or a salt thereof.

In some embodiments, the composition comprises a molar ratio of **Compound 2-9** to **Compound 2-9c**, or a salt thereof, that is substantially 1:1.

In some embodiments, the composition comprises a molar ratio of **Compound 2-9** to **Compound 2-9c**, or a salt thereof, that is about 1:1 to about 99:1; about 1:1 to about 95:1; about 1:1

to about 90:1; about 1:1 to about 85:1; about 1:1 to about 80:1; about 1:1 to about 75:1; about 1:1 to about 70:1; about 1:1 to about 65:1; about 1:1 to about 60:1; about 1:1 to about 55:1; about 1:1 to about 50:1; about 1:1 to about 45:1; about 1:1 to about 40:1; about 1:1 to about 35:1; about 1:1 to about 30:1; about 1:1 to about 25:1; about 1:1 to about 20:1; about 1:1 to about 15:1; about 1:1 to about 10:1; about 1:1 to about 5:1; or about 1:1 to about 2:1.

One aspect of the present disclosure is a compound selected from:

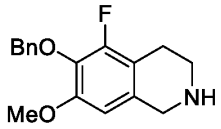
6-(benzyloxy)-5-fluoro-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**Compound 2-6**);

6-(benzyloxy)-5-fluoro-7-methoxy-3,4-dihydroisoquinoline (**Compound 2-7**); and

(2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 2-10**);

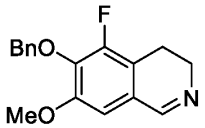
or a salt thereof.

In some embodiments, the compound is 6-(benzyloxy)-5-fluoro-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**Compound 2-6**), or a salt thereof;



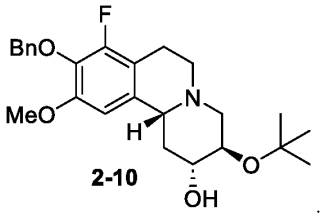
2-6

In some embodiments, the compound is 6-(benzyloxy)-5-fluoro-7-methoxy-3,4-dihydroisoquinoline (**Compound 2-7**), or a salt thereof;



2-7

In some embodiments, the compound is (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 2-10**), or a salt thereof;



2-10

It is further appreciated that certain features, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

PHARMACEUTICAL COMPOSITIONS, FORMULATION, AND DOSAGE FORMS

The present disclosure further provides for pharmaceutical products, such as, pharmaceutical compositions, formulations, unit dosage forms, and kits; each comprising a compound, as described herein, or a pharmaceutically acceptable salt thereof.

The present disclosure further provides for pharmaceutical compositions comprising a compound, as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient for use in the methods described here, such as, for treating hyperkinetic movement disorders. A pharmaceutically acceptable excipient is a physiologically and pharmaceutically suitable non-toxic and inactive material or ingredient that does not interfere with the activity of the drug substance; an excipient also can be called a carrier. The formulation methods and excipients described herein are exemplary and are in no way limiting. Pharmaceutically acceptable excipients are well known in the pharmaceutical art and described, for example, in Rowe *et al*., Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5th Ed., 2006, and in Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to an VMAT2 inhibitor, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art can further formulate the VMAT2 inhibitor in an appropriate manner, and in accordance with accepted practices, such as, those disclosed in Remington, *supra*.

Methods of administration include systemic administration of a VMAT2 inhibitor described herein, preferably in the form of a pharmaceutical composition as discussed above. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions.

Pharmaceutical preparations for oral administration can be obtained by any suitable method, typically by uniformly mixing the compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, processing the mixture, after adding suitable auxiliaries, if desired, forming the resulting mixture into a desired shape to obtain tablets or dragee cores.

Conventional excipients, such as, binding agents, fillers, adjuvant, carrier, acceptable wetting agents, tableting lubricants, and disintegrants can be used in tablets and capsules for oral administration. Liquid preparations for oral administration can be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations can be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Parenteral dosage forms can be prepared by dissolving the compound in a suitable liquid vehicle and filter sterilizing the solution before lyophilization, or simply filling and sealing an appropriate vial or ampule.

Some embodiments provide methods for preparing a pharmaceutical composition comprising the step of admixing a compound, as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams, or sprays containing in addition to the drug substance such carriers as are known in the art to be appropriate.

In making pharmaceutical compositions, the drug substance is typically mixed (*i.e.*, admixed) with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier, or medium for the drug substance. Thus, the compositions can be in the form of tablets, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

For preparing solid form pharmaceutical compositions, such as, powders, tablets, capsules, cachets, suppositories, and dispersible granules an excipient can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

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

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent.

Pharmaceutical compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and can contain formulatory agents, such as, suspending, stabilizing and/or dispersing agents. Alternatively, the pharmaceutical compositions can be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, *e.g.*, sterile, pyrogen-free water, before use.

The pharmaceutical compositions can be formulated as an aqueous solution, an aqua-alcoholic solution, a solid suspension, an emulsion, a liposomal suspension, or a freeze-dried powder for reconstitution. Such pharmaceutical compositions can be administered directly or as an admixture for further dilution/reconstitution. Route of administration includes intravenous bolus, intravenous infusion, irrigation, and instillation.

Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided drug substance in water with viscous material.

For topical administration to the epidermis the compounds described herein, or pharmaceutically acceptable salts thereof can be formulated as gels, ointments, creams, or lotions, or as a transdermal patch. Also, formulations suitable for topical administration in the mouth include lozenges comprising drug substance in a flavored base.

Solutions or suspensions can be applied directly to the nasal cavity by conventional means, for example with a dropper, pipette, or spray. The formulations can be provided in single or multi-dose form. In the latter case of a dropper or pipette, this can be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this can be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract can also be achieved by means of an aerosol formulation provided in a pressurized pack with a suitable propellant. If the compounds described herein, or pharmaceutically acceptable salts thereof or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler, or a dry powder inhaler.

Alternatively, the pharmaceutical composition can be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable, powder base, such as, lactose, starch, starch derivatives. Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, *e.g.*, gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The compounds, as described herein, or pharmaceutically acceptable salts thereof, can also be administered via a rapid dissolving or a slow-release composition, wherein the composition includes a biodegradable rapid dissolving or slow-release carrier.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the drug substance. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as, packeted tablets, capsules, and powders in vials or ampoules. Also, the unit

dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. In some embodiments, the pharmaceutical preparation is a tablet or capsule for oral administration. In some embodiments, the pharmaceutical preparation is a liquid formulated for intravenous administration.

The compositions can be formulated in a unit dosage form, each dosage containing the drug substance or equivalent mass of the drug substance. The term "unit dosage forms" refers to physically discrete units of a formulation suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable excipient, as described herein.

The liquid forms including the drug substance can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils.

The pharmaceutical compositions described herein can be sterilized by conventional sterilization techniques, or can be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous, or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable excipients as described herein. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device, or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more-unit dosage forms containing the drug substance. The pack may for example comprise metal or plastic foil, such as, a blister pack. The pack or dispenser device can be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, can be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

For preparing solid compositions, such as tablets, the drug substance can be mixed with an excipient to form a solid preformulation composition containing a homogeneous mixture of components. When referring to these preformulation compositions as homogeneous, the drug substance is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms, such as, tablets and capsules.

Kits with unit doses of one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof, usually in oral or injectable doses, are provided. Such kits can include a container containing the unit dose, an informational package insert describing the use and attendant benefits of the drugs in treating pathological condition of interest, and optionally an appliance or device for delivery of the composition.

The compounds described herein, or a pharmaceutically acceptable salt thereof, can be effective over a wide dosage range and are generally administered in a therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual subject, the severity of the subject's symptoms, and the like.

The amount of compound or composition administered to a subject will also vary depending upon what is being administered, the purpose of the administration, such as, prophylaxis or therapy, the state of the subject, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a subject already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptomology and/or pathology of the disease and its complications. Therapeutically effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors, such as, the severity of the disease, the age, weight, and general condition of the subject, and the like.

The desired dose may conveniently be presented in a single dose or presented as divided doses administered at appropriate intervals, for example, as two, three, four, or more sub-doses per day. The sub-dose itself can be further divided, *e.g.*, into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example two, three, or four-part administrations. If appropriate, depending on individual behavior, it can be necessary to deviate upward or downward from the daily dose indicated.

It will be apparent to those skilled in the art that the dosage forms described herein can comprise a compound described herein or pharmaceutically acceptable salt thereof.

PREPARATIONS

As used herein, a "preparation" is the product of a process used to make or isolate a compound as disclosed and described herein, wherein the preparation contains at least one other

component in addition to the compound. In some embodiments, the preparation comprises a chemical entity.

As used herein, a "chemical entity" defined in the context of a "preparation," refers to a compound as disclosed and described herein and at least one other component in addition to the compound. For example, a chemical entity can be a co-crystal or salt of a compound as disclosed and described herein.

Some embodiments provide a preparation comprising a compound as disclosed and described herein. In some embodiments, the compound is a component of a chemical entity. In some embodiments, the chemical entity is a salt of a compound as disclosed and described herein. In some embodiments, the chemical entity is a (2*S*,3*S*)-2,3-bis(4-methylbenzoyloxy)butanedioic acid (DPTTA) salt of a compound as disclosed and described herein.

In some embodiments, the compound of the preparation is in at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, 99.5%, 99.9%, or 100% enantiomeric excess, or an enantiomeric excess within a range defined by any of the preceding numbers. In some embodiments, the compound of the preparation is in at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or 100% enantiomeric excess, or an enantiomeric excess within a range defined by any of the preceding numbers.

In some embodiments, the compound of the preparation is in at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 99.9% diastereomeric excess, or a diastereomeric excess within a range defined by any of the preceding numbers. In some embodiments, the compound of the preparation is in at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% diastereomeric excess, or a diastereomeric excess within a range defined by any of the preceding numbers.

In some embodiments, the preparation comprises at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 93% by weight of the compound, or a % by weight within a range defined by any of the preceding numbers. In some embodiments, the preparation comprises at least 50%, 60%, 70%, 80%, 90%, or 93% by weight of the compound, or a % by weight within a range defined by any of the preceding numbers. In some embodiments, the preparation comprises at most 50%, 60%, 70%, 80%, 90%, 93%, or 95% by weight of the compound, or a % by weight within a range defined by any of the preceding numbers.

In some embodiments, the preparation comprises at least 50% by weight of the compound. In some embodiments, the preparation is in the form of a solid, *i.e.*, a solid preparation. In some embodiments, the preparation is used to prepare a pharmaceutical composition.

METHODS OF USE

The compounds, as described herein, are inhibitors of VMAT2. Accordingly, the present disclosure includes a method of inhibiting VMAT2 (*i.e.*, decreasing at least one function of VMAT2

or decreasing expression of VMAT2) by contacting the VMAT2 with a compound as disclosed and described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting can occur *in vitro*, such as, where the VMAT2 is located in a purified preparation or in a cell outside of a living organism (*e.g.*, in a tissue sample or a cellular preparation). In some embodiments, the contacting can occur *in vivo*, such as, where the VMAT2 is located in a living organism.

The VMAT2 inhibitors described herein can reduce the level of monoamines in the central nervous system. Accordingly, the present disclosure includes a method of reducing the level of monoamines in the central nervous system of a subject comprising administering to the subject an amount of a compound, as described herein, or a pharmaceutically acceptable salt thereof, sufficient to lower the level of monoamines relative to the level prior to administration.

The VMAT2 inhibitors as disclosed and described herein are believed to have utility over a wide range of therapeutic applications, and may be used to treat or prevent a variety of disorders which are caused by or linked to inhibition of the human vesicular monoamine transporter isoform 2. These disorders include neurological and psychiatric disorders, for example, hyperkinetic movement disorders, schizophrenia, and mood disorders. A compound, as described herein, or a pharmaceutically acceptable salt thereof, can be used in any of the therapeutic methods disclosed and described herein.

Accordingly, in various embodiments as disclosed herein, methods are provided for treating or preventing a neurological and/or psychiatric disease or disorder in a subject in need thereof by administering to the subject a pharmaceutically effective amount of a VMAT2 inhibitor as described herein, or a pharmaceutically acceptable salt thereof. The neurological and/or psychiatric disease or disorder can be, for example, a hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder (*e.g.*, restricted and repetitive behaviors associated with Autism spectrum disorder (ASD)), Rett syndrome, or chorea-acanthocytosis.

In various other embodiments as disclosed herein, methods are provided for treating or preventing a vesicular monoamine transporter-2 (VMAT2) disease or disorder in a subject in need thereof by administering to the subject a pharmaceutically effective amount of a VMAT2 inhibitor as described herein, or a pharmaceutically acceptable salt thereof. The VMAT2 disease or disorder can be, for example, an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington's disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function

disorder; a Parkinson's/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

Accordingly, in various embodiments as disclosed herein, methods are provided for treating or preventing a hyperkinetic movement disorder in a subject in need thereof by administering to the subject in need thereof a pharmaceutically effective amount of a VMAT2 inhibitor described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the hyperkinetic movement disorder is tardive dyskinesia, Tourette's syndrome, Huntington's disease, chorea associated with Huntington's disease, or tics. In other embodiments, the hyperkinetic movement disorder is ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, or tremors.

In some embodiments, methods are provided for treating or preventing a mood disorder in a subject in need thereof by administering to the subject in need thereof a pharmaceutically effective amount of a VMAT2 inhibitor described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the mood disorder is bipolar disorder, major depressive disorder, mania in a mood disorder, or depression in a mood disorder.

In some embodiments as disclosed herein, methods are provided for treating or preventing schizophrenia or schizoaffective disorder in a subject in need thereof by administering to the subject in need thereof a pharmaceutically effective amount of a VMAT2 inhibitor described herein, or a pharmaceutically acceptable salt thereof.

In some embodiments, the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.

In some embodiments, the hyperkinetic movement disorder is tardive dyskinesia.

In some embodiments, the hyperkinetic movement disorder is Tourette's syndrome.

In some embodiments, the hyperkinetic movement disorder is Huntington's disease.

In some embodiments, the hyperkinetic movement disorder is tics.

In some embodiments, the hyperkinetic movement disorder is chorea associated with Huntington's disease.

In some embodiments, the hyperkinetic movement disorder is ataxia, chorea, dystonia, hemifacial spasm, Huntington's disease, myoclonus, restless leg syndrome, or tremors.

In some embodiments, the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder.

In some embodiments, the neurological or psychiatric disease or disorder is schizophrenia.

In some embodiments, the neurological or psychiatric disease or disorder is schizoaffective disorder.

In some embodiments, the neurological or psychiatric disease or disorder is obsessive-compulsive disorder.

In some embodiments, the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder.

In some embodiments, the neurological or psychiatric disease or disorder is autism spectrum disorder.

In some embodiments, the neurological or psychiatric disease or disorder is irritability associated with autism spectrum disorder.

In some embodiments, the neurological or psychiatric disease or disorder is agitation associated with any one or more neurological or psychiatric disease or disorder described herein.

In some embodiments, the neurological or psychiatric disease or disorder is restricted and repetitive behaviors associated with autism spectrum disorder (ASD).

In some embodiments, the neurological or psychiatric disease or disorder is obsessions and compulsions in partial and non-responders (or completely refractory) with obsessive-compulsive disorder (OCD). In some embodiments, the neurological or psychiatric disease or disorder is obsessions and compulsions in partial and non-responders (or completely refractory) with obsessive-compulsive disorder (OCD) and the compounds described herein are administered as adjunctive therapy. In some embodiments, compounds described herein are useful as an adjunctive therapy or adjunctive treatment of schizophrenia. In some embodiments, the compounds described here are administered as adjunctive therapy with the primary therapy being treatment with antidepressants.

In some embodiments, the neurological or psychiatric disease or disorder is Bipolar I Disorder. In some embodiments, the compound described herein is administered as monotherapy for the treatment of Bipolar I Disorder. In some embodiments, the compound described herein is administered as maintenance therapy for the treatment of Bipolar I Disorder. In some embodiments, the compound described herein is administered as monotherapy maintenance therapy for the treatment of Bipolar I Disorder.

In some embodiments, the compound, as described herein, or a pharmaceutically acceptable salt thereof, is administered to the patient to treat or prevent a disease or disorder selected from:

ataxias or spinal muscular atrophies, such as, spinocerebellar ataxia type 17 (SCA17) / HDL4, ataxia, spinal muscular atrophy, amyotrophic lateral sclerosis, familial amyotrophic lateral sclerosis, bulbospinal muscular atrophy congenital, dentatorubral-pallidoluysian atrophy, hereditary motor neuron disease, and hereditary spastic paraplegia;

chorea, such as, benign hereditary chorea, chorea, chorea associated with mitochondrial disease/causes, chorea associated with Wilson's disease, chorea gravidarum, chorea-acanthocytosis, drug-induced chorea, hemiballism, rheumatic/Sydenham's chorea, and thyrotoxic chorea/hyperthyroid chorea;

congenital malformations, deformations, or abnormalities, such as, Angelman syndrome, congenital neurological disorder, Aicardi’s syndrome, neurofibromatosis, congenital facial nerve hypoplasia, Moebius II syndrome, Cockayne’s syndrome, Sjogren-Larsson syndrome, Laurence-Moon-Bardet-Biedl syndrome, Fragile X syndrome, and Prader-Willi syndrome;

dementia, such as, AIDS-related dementia, Alzheimer's disease, congenital neurological degeneration, Lewy body dementia, micro-infarct dementia, pre-senile dementia, senile dementia, irritability associated with dementia, and vascular dementia;

diseases of oral cavity, salivary glands, and jaws, such as, glossodynia / burning mouth syndrome and temporomandibular joint disorder;

dyskinesia, such as, pharyngeal dyskinesia, dyskinesia, dyskinesia (neonatal), dyskinesia (oesophageal), levodopa-induced dyskinesia, paroxysmal kinesigenic dyskinesias, paroxysmal nonkinesigneic dyskinesias, and respiratory dyskinesia;

dystonia, such as, blepharospasm, buccoglossal syndrome, drug-induced acute dystonia, dystonia, early onset primary dystonia, genetic torsion dystonia, hand dystonia/writer's cramp, idiopathic nonfamilial dystonia, idiopathic orofacial dystonia/Meige's disease, laryngeal dystonia, oromandibular dystonia, and spasmodic torticollis/cervical dystonia;

endocrine, nutritional, and metabolic diseases, such as, Wilson’s Disease, diabetes mellitus, obesity, syndrome X, and Lesch-Nyhan syndromes;

epilepsy, such as, Baltic myoclonic epilepsy, benign familial neonatal convulsions, epilepsy, epilepsy congenital, Lafora’s myoclonic epilepsy, severe myoclonic epilepsy of infancy, and convulsions;

habit and impulse disorders, such as, binge eating disorder, kleptomania, impulse control disorders, trichotillomania, intermittent explosive disorder, pathological gambling, and pyromania;

Huntington’s disease or related disorders, such as, Huntington’s disease, Huntington's disease-like syndromes 1-3, Huntington's chorea, and X-linked McLeod Neuroacanthocytosis syndrome;

mood or psychotic disorders, such as, schizophrenia, psychosis, mania, bipolar disorder, depression, and mood disorders;

other diseases or disorders, such as, fumbling, hypokinesia, hypokinesia (neonatal), movement disorder, rabbit syndrome, spasticity, up and down phenomenon, asthma, cancer, congenital nystagmus, familial hemiplegic migraine, fetal movement disorder, and rheumatoid arthritis;

neurotic, stress-related, and somatoform disorders, such as, social anxiety disorder, panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and psychogenic movement disorder;

other degenerative diseases of basal ganglia, such as, pantothenate kinase-associated neurodegeneration, progressive supranuclear palsy, multiple system atrophy, dyslexia, basal ganglion degeneration, and neuroferritinopathy;

other extrapyramidal and movement disorders, such as, hemiballismus, extrapyramidal disorder, essential tremor, geniospasm, hyperexplexia, akathisia, ballismus / hemiballism, myoclonus, and restless legs syndrome / Willis-Ekbom's syndrome;

other nervous system or motor function, such as, sleep-related bruxism, abnormal involuntary movement disorders, alien limb syndrome, Alzheimer's disease (agitation), clumsiness, clonic hemifacial spasm, olfactory nerve agenesis, congenital cranial nerve paralysis, exercise ataxia syndrome, familial periodic paralysis, congenital hemiparesis, fine motor delay, fine motor skill dysfunction, gross motor delay, multiple sclerosis, congenital flaccid paralysis, congenital Horner's syndrome, alternating hemiplegia of childhood, motor developmental delay, cerebral palsy, athetoid cerebral palsy, posturing, pseudoparalysis, psychomotor hyperactivity, bradykinesia, synkinesis, akinesia, Riley-Day syndrome, and athetosis;

Parkinson's/parkinsonism, such as, parkinsonism, drug-induced parkinsonism, micrographia, and Parkinson's disease;

pediatric-onset behavioral and emotional disorders, such as, attention deficit hyperactivity disorder, attention deficit disorder, hyperkinesia, hyperkinesia (neonatal), oppositional defiant disorder, provisional tic disorder, persistent (chronic) motor or vocal tic disorder, stereotypic movement disorder, stereotypy, and Tourette's syndrome;

pervasive developmental disorders, such as, autism spectrum disorders, Rett's syndrome, Asperger's syndrome, pervasive developmental disorder NOS, and dyslexia; and

substance abuse or dependence, such as, addiction disorders, alcoholism, cocaine dependence, illegal drug abuse, methamphetamine abuse, methamphetamine addiction/dependence, methamphetamine use disorder, morphine abuse, morphine-analogue abuse, nicotine dependence, polysubstance abuse, and prescription drug abuse.

In some embodiments, the compound, as described herein, or a pharmaceutically acceptable salt thereof, is administered to the patient to treat or prevent a palsy. In some embodiments, the palsy is selected from: spastic cerebral palsy (including, but not limited to, spastic hemiplegia cerebral palsy, spastic diplegia cerebral palsy, and spastic quadriplegia cerebral palsy), dyskinetic cerebral palsy, ataxic cerebral palsy, and "mixed types" cerebral palsy.

In some embodiments, the palsy is spastic cerebral palsy.

In some embodiments, the palsy is dyskinetic cerebral palsy.

In some embodiments, the palsy is ataxic cerebral palsy.

In some embodiments, the palsy is "mixed types" cerebral palsy.

The phrase "mixed types" cerebral palsy includes a mix of symptoms associated with other types of cerebral palsies.

In some embodiments, the patient which is treated has been determined to have 22q11.2 deletion syndrome. In some embodiments, the patient is predisposed to developing a psychiatric disorder due to the patient having 22q11.2 deletion syndrome. In some embodiments, the patient has been determined to have COMT haploinsufficiency. In some embodiments, the patient is predisposed to developing a psychiatric disorder due to the patient having COMT haploinsufficiency.

In another embodiment, the VMAT2 inhibitors described herein may be hydrolyzed in the body of a mammal to compounds that may inhibit the human vesicular monoamine transporter isoform 2. As such, these VMAT2 inhibitors may have additional utility in altering the *in vivo* properties of the metabolite in a mammal, such as, the maximum concentration or duration of action.

Characterizing any of the VMAT2 inhibitors described herein may be determined using methods described herein, and those in the art. For example, dopamine depletion may be determined using the locomotor activity (LMA) assay. Another *in vivo* animal model includes the conditioned avoidance response (CAR) test, which has been shown to be an effective and reliable preclinical model for assessing the antipsychotic activity of compounds.

COMBINATION THERAPY

The compounds of the present disclosure, and their pharmaceutically acceptable salts, can be used as monotherapy, or in combination with one or more other pharmaceutical agents. In some embodiments, a compound, as described herein, or its pharmaceutically acceptable salt, is administered together with (simultaneously or sequentially) one or more pharmaceutical agents selected from antidepressants, antipsychotics (typical or atypical), antiepileptics, antimicrobials, antiarrhythmics, mood stabilizers, and gastrointestinal drugs. In some embodiments, a compound, as described herein, or a pharmaceutically acceptable salt thereof, is used in adjunctive therapy which refers to a treatment that is used in conjunction with a primary treatment and its purpose is to assist the primary treatment. Adjunctive therapies are typically co-administered therapies. As an example of adjunctive therapy, if obsessive-compulsive disorder is being treated, the primary therapy may be, *e.g.*, an antidepressant, and the co-administration of a compound described herein would be considered an adjunctive therapy.

COMPOUND SYNTHESIS

Detailed compound synthesis methods are described herein in the Examples. In general, starting components are commercially available chemicals and may be obtained from commercial sources or may be made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature.

In general, the compounds used in the reactions described herein may be made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. Methods known to one of ordinary skill in the art may be identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds of the present disclosure, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York; S. R.

Sandler *et al.*, "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," 4th Ed., Wiley-Interscience, New York, 1992.

Specific and analogous reactants may also be identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., may be contacted for more details). Chemicals that are known but not commercially available in catalogs may be prepared by custom chemical synthesis houses according to known methods, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services.

EXAMPLES

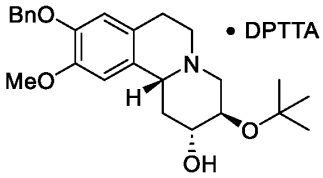
The following examples are included to demonstrate embodiments of the disclosure. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure. Additional illustrated syntheses for compounds of the present invention are shown in the accompanying Figures where the symbols have the same definitions as used throughout this disclosure.

Analytical HPLC analyses were performed on a liquid chromatography-mass spectrometry (LCMS) system with a UV Detector (Thermo™ Vanquish™ VF-D11-A UV/VIS Detector), Charged Aerosol Detector (Thermo™ Vanquish™ VH-D20-A), and mass spectrometer (Thermo™ ISQ-EC). Reverse-phase preparative HPLC purifications were performed on an LCMS system C_{18} Kinetix 5µ 100 A 150 x 21.2 mm column by Phenomenex using ACN/water gradient containing 0.1% TFA. Supercritical fluid chromatography purification (SFC) was performed using a Waters™ Prep 100q™ system, equipped with a UV Detector (Waters™ 2998 Photodiode Array Detector™) and mass spectrometer (Waters™ Acquity QDa Detector™). A Waters™ Viridis™ BEH 2-Ethylpyridine 130 Å 5 µm, 30 mm x 100 mm column was used with a CO2 and 0.3% NH_4OH in MeOH gradient, run at 100 mL/min, 40°C, and 105 bar back pressure regulator. All final compounds were analyzed by analytical HPLC utilizing a Waters™ Acquity™ UPLC HSS T3 100A 50 x 2.1mm column, and peaks were monitored using charged aerosol detection, mass spectrometry and UV at 210, 254, and 280 nm for purity.

^{1}H was recorded in an appropriate NMR solvent, such as, dimethylsulfoxide-d_6 (DMSO-d_6), on a Bruker 400 MHz spectrometer equipped with a Broad Band NMR probe, or on a Bruker 500 MHz spectrometer equipped with a 5 mm QNP probe with Z gradient. The ^{1}H chemical signals are given in parts per million (ppm) with the residual solvent signal used as reference. The chemical shifts

are expressed in ppm (δ) and coupling constants (J) are reported in hertz (Hz). Reactions were performed under an atmosphere of dry nitrogen unless otherwise stated.

EXAMPLE 1: Preparation of the salt of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol and (2*S*,3*S*)-2,3-bis(4-methylbenzoyloxy)butanedioic acid (Compound 1-8·DPTTA).



To a solution of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound (±)-1-7**, 0.166 g, 0.403 mmol, 1.0 eq) in MeOH (2 mL) was added (2*S*,3*S*)-2,3-bis(4-methylbenzoyloxy)butanedioic acid (DPTTA, 0.156 g, 0.403 mmol, 1.0 eq). The mixture was heated to 50°C with stirring and held at that temperature for 10 min. The mixture was cooled to rt then concentrated *in vacuo* to give an off-white solid. The salt pair was suspended in EtOH (4 mL) and heated with stirring to 70°C to give a suspension. MeOH (3 mL) was added, and the mixture stirred at 70°C, at which point the mixture became a clear solution. The sample was cooled to RT with stirring over 30 min then stirred overnight at RT. The resulting precipitate was collected by vacuum filtration and rinsed with EtOH (0.5 mL) and dried to provide **Compound 1-8·DPTTA** (0.116 g, 0.145 mmol, 36%) as a white solid. Chiral purity analysis was performed using a Waters™ Ultra-Performance Convergence Chromatography (UPC2)™ supercritical fluid chromatography (SFC) system, equipped with a UV Detector (WatersTM Acquity UPC2 PDA Detector™) and mass spectrometer (Waters™ Acquity QDa Detector™). A Chiral Technologies Inc™ ChiralPak™ IBU/SFC 1.6 μm, 2.1 mm x 50 mm column was used with an isocratic gradient at 95% CO_2 and 5% 0.5% DMEA in MeOH, at 1.5 mL/min, 40°C, and 1500 psi back pressure regulator. An extracted wavelength of 281 nm was used for %ee quantification and analysis. An optical purity of 100% ee as a single diastereomer was determined by chiral SFC analysis. The assigned structure was confirmed by a single crystal x-ray structure.

Single Crystal X-Ray Structure of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol DPTTA salt (**Compound 1-8·DPTTA**).

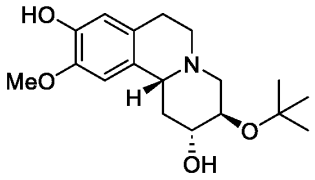
(2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol DPTTA salt (**Compound 1-8·DPTTA**, < 1 mg) was combined with a 50:50 EtOH/MeOH mixture (0.2 mL). The sample was heated to approximately 50°C in a capped vial to obtain a clear solution, which was then allowed to cool to RT. The solution remained clear after 2d at RT and was allowed to evaporate slowly. In 3d, the solution was found to contain blocks of single crystal quality.

The crystal structure of **Compound 1-8·DPTTA** was determined to be a mixed ethanol and methanol solvate with formula $C_{25}H_{34}NO_4 \cdot C_{20}H_{17}O_8 \cdot 0.851(C_2H_6O) \cdot 0.149(CH_4O)$. The solvate was refined as disordered between majority ethanol and minority methanol. Chiral centers at N1 (protonated), C2, C3, and C5 were all determined to have *R* configuration. Chiral centers at C27 and C28 (*O*,*O*'-di-*p*-toluoyl-tartaric acid) both have *S* configuration. The unit system and space group for **Compound 1-8·DPTTA** are shown in **Table 1**. Data collection and refinement parameters for **Compound 1-8·DPTTA** are shown in **Table 2**.

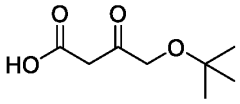
Table 1: Crystal Data for Compound 1-8·DPTTA (2*R*,3*R*,11b*R*)	
Chemical formula	$C_{25}H_{34}NO_4 \cdot C_{20}H_{17}O_8 \cdot 0.851(C_2H_6O) \cdot 0.149(CH_4O)$
Mr	841.85
Crystal system, Space group	Triclinic, P1
Data collection temperature (K)	150
a (Å)	8.7578 (3)
b (Å)	9.9558 (3)
c (Å)	13.5223 (5)
α (°)	76.7098 (17)
β (°)	74.5003 (16)
γ (°)	80.0520 (17)
volume (Å3)	1097.90 (7)
Z	1
Radiation type	Cu Kα
Crystal shape	Block
Color	Colorless
Crystal size (mm)	0.19 × 0.10 × 0.08

Table 2: Data collection and Refinement Parameters for Compound 1-8·DPTTA (2*R*,3*R*,11b*R*)	
Diffractometer	Bruker AXS D8 Quest diffractometer with PhotonIII_C14 charge-integrating and photon counting pixel array detector
Radiation source	I-mu-S microsource X-ray tube
Absolute structure parameter	-0.03 (8)

EXAMPLE 2: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (Compound 1-9, see also International Application No. PCT/US2023/033206).

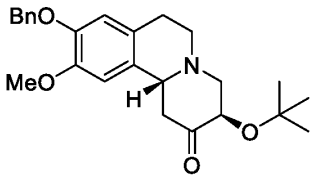


Step 1: Preparation of 4-(*tert*-butoxy)-3-oxobutanoic acid (Compound 1-2).



To a mixture of ethyl 4-(*tert*-butoxy)-3-oxobutanoate (**Compound 1-1**, 39.4 g, 195 mmol, 1.0 eq) and water (600 mL) was added aq. NaOH (6 N, 68.3 mL, 410 mmol, 2.1 eq) and the resulting mixture stirred at RT overnight. The mixture was cooled to 0°C then acidified with concentrated H_2SO_4 to pH 1-2. The aqueous layer was extracted five times with MTBE. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude 4-(*tert*-butoxy)-3-oxobutanoic acid (**Compound 1-2**, 33.1 g 190 mmol, 97%) as a clear brown oil that was carried on without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.53 (bs, 1H), 4.05 (s, 2H), 3.43 (s, 2H), 1.14 (s, 9H).

Step 2: Preparation of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (Compound (±)-1-5).

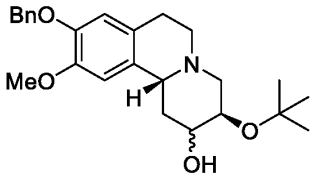


To a solution of 6-(benzyloxy)-7-methoxy-3,4-dihydroisoquinoline hydrochloride (CAS Registry Number: 68360-23-6; **Compound 1-3**, 28.9 g, 95 mmol, 1.0 eq) in water (289 mL) was added NaOAc (0.779 g, 9.50 mmol, 0.1 eq) at 50°C. A solution of 4-(*tert*-butoxy)-3-oxobutanoic acid (**Compound 1-2**, 33.1 g, 190 mmol, 2.0 eq) was added dropwise and the mixture was stirred at 50°C for 3h. The mixture was cooled to RT and quenched with saturated aq. $NaHCO_3$. The aqueous layer was extracted three times with MTBE. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude (±)-1-(6-(benzyloxy)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(*tert*-butoxy)propan-2-one (**Compound 1-4**) as a brown oil. To a solution of the crude material in MeOH (378 mL) was added acetic acid (5.4 mL, 95 mmol, 1.0 eq) and 37% (w/w) aq. formaldehyde (6.6 mL, 80.8 mmol, 0.85 eq). The mixture was stirred at 40°C overnight. The mixture was cooled to RT, quenched with saturated aq. $NaHCO_3$, and extracted three times with DCM. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Two silica gel columns (330 g) were loaded using DCM and run with an increasing gradient of EtOAc (0-50% over 20 min) in hexanes to afford (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (**Compound (±)-1-5**, 13.1 g, 32.0 mmol, 34% over two steps) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.46-7.31 (m, 5H), 6.81 (s, 1H), 6.75 (s, 1H), 5.03 (s, 2H), 4.37 (dd, J = 10.9, 7.0 1H), 3.74 (s, 3H), 3.46 (br d, J =

11.9 Hz, 1H), 3.23-3.09 (m, 2H), 2.95-2.84 (m, 2H), 2.70-2.62 (m, 1H), 2.59-2.42 (m, 3H), 1.15 (s, 9H).

(Reduction, Method A)

Step 3A: Preparation of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-*2H*-pyrido[2,1-*a*]isoquinolin-2-ol (Compound (±)-1-6).



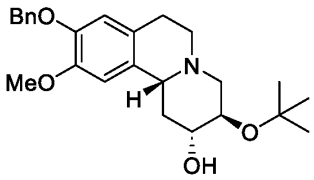
To a solution of 9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (**Compound (±)-1-5**, 10.9 g, 26.6 mmol, 1.0 eq) in MeOH (110 mL) at 0°C was added $NaBH_4$ (2.01 g, 53.2 mmol, 2.0 eq) in portions. The mixture was stirred 30 min then warmed to RT and stirred 1h. The reaction mixture was diluted with water (100 mL) and aq. NaOH (1M, 100 mL) then extracted three times with DCM. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A silica gel column (220 g) was loaded using DCM and run with an increasing gradient of EtOAc (0-80% over 20 min) in hexanes to afford (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound (±)-1-6**) as a 1.4:1 mixture of diastereomers (8.64 g, 21.0 mmol, 79%).

(Reduction, Method B)

Step 3B: Preparation of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-*2H*-pyrido[2,1-*a*]isoquinolin-2-ol (Compound (±)-1-6).

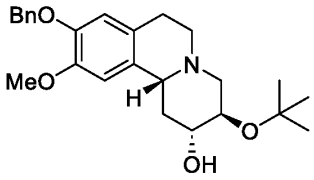
To a solution of 9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (**Compound (±)-1-5**, 11.7 g, 28.5 mmol, 1.0 eq) in THF (184 mL) at 0°C was added DIBAL-H (1.0 M in hexanes, 42.8 mL, 42.8 mmol, 1.5 eq) dropwise. The mixture was stirred 1h at 0°C. The reaction mixture was quenched with acetone. The mixture was diluted with aq. Rochelle's salt (10% w/w) and stirred vigorously for 30 min. The mixture was extracted three times with DCM. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound (±)-1-6**) as a 6.5:1 mixture of diastereomers (11.70 g, 28.4 mmol, 99%) that was carried on directly to the next step (*i.e.*, synthesis of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol **Compound 1-8**).

Step 3C: Preparation of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (Compound (±)-1-7).



Diastereomerically pure **Compound (±)-1-7** can be obtained by chromatography of **Compound (±)-1-6** (0.432 g, 1.05 mmol, 1.4:1 dr). A silica gel column (4 g) was loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 20 min) in hexanes to afford (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound (±)-1-7**, 166 mg, 0.403 mmol, 38%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.45-7.41 (m, 2H), 7.41-7.37 (m, 2H), 7.34-7.31 (m, 1H), 6.77 (s, 1H), 6.74 (s, 1H), 5.01 (s, 2H), 4.61 (d, J = 4.7 Hz, 1H), 3.73 (s, 3H), 3.32-3.27 (m, 2H), 3.02 (br d, J = 11.0 Hz, 1H), 2.92-2.82 (m, 3H), 2.54-2.45 (m, 2H), 2.35-2.29 (m, 1H), 2.04 (br t, J = 10.3 Hz, 1H), 1.27-1.21 (m, 1H), 1.17 (s, 9H).

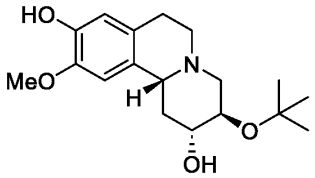
Step 4: Preparation of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (Compound 1-8).



To a solution of crude (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound (±)-1-6**, 6.5:1 dr, 11.70 g, 28.5 mmol, 1 eq) in EtOH (250 mL) was added (2*S*,3*S*)-2,3-bis(4-methylbenzoyloxy)butanedioic acid (DPTTA, 11.00 g, 28.5 mmol, 1.0 eq). The solution was heated to reflux with stirring which became a suspension upon heating. After the addition of MeOH (60 mL) the mixture was held at reflux until a clear solution was obtained. The solution was cooled to 75°C, then seeded with **Compound 1-8·DPTTA** (0.050 g, see **EXAMPLE 1**) and held at constant temperature for 1h 30 min. The mixture was cooled at a rate of 8°C per h to RT, then continued stirring for two days. The resulting precipitate was collected by vacuum filtration and dried to provide **Compound 1-8·DPTTA** (7.357 g, 6.26 mmol, 32% over two steps from **Compound (±)-1-5**, prepared in **EXAMPLE 2**, **Step 2** above) as a white solid. An optical purity of 100% ee was determined by chiral supercritical fluid chromatography (SFC) analysis and a diastereomeric purity ≥ 99%. The chiral salt pair was suspended in DCM and water was added. The mixture was basified with saturated aq. NH_4OH until pH ~ 10. The mixture was extracted three times with DCM. The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound 1-8**, 3.78 g, 6.12 mmol, 32% over two steps from **Compound (±)-1-5**, prepared in **EXAMPLE 2**, **Step 2** above) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.45-7.41 (m, 2H), 7.41-7.37 (m, 2H), 7.34-7.31

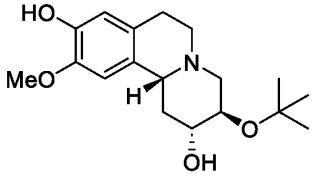
(m, 1H), 6.77 (s, 1H), 6.74 (s, 1H), 5.01 (s, 2H), 4.61 (d, J = 4.7 Hz, 1H), 3.73 (s, 3H), 3.32-3.27 (m, 2H), 3.02 (br d, J = 11.0 Hz, 1H), 2.92-2.82 (m, 3H), 2.54-2.45 (m, 2H), 2.35-2.29 (m, 1H), 2.04 (br t, J = 10.3 Hz, 1H), 1.27-1.21 (m, 1H), 1.17 (s, 9H).

Step 5: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (Compound 1-9).

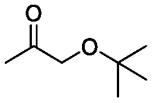


To a solution of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound 1-8**, 1.950 g, 4.74 mmol, 1.0 eq) in 3:1 MeOH:H_2O (20 mL) was added aq. HCl (12.1 M, 0.47 mL, 5.69 mmol, 1.2 eq) dropwise at 0°C with stirring. The mixture was stirred 10 min. Palladium on carbon (10% w/w, 0.252 g, 0.237 mmol, 0.05 eq) and ammonium formate (2.988 g, 47.4 mmol, 10 eq) were added and mixture was stirred at 50°C for 30 min. The mixture was cooled to 0°C and acidified to pH = 1 with aq. HCl (12.1 M). The suspension was filtered, and solids rinsed with MeOH (4 mL). The filtrate was transferred to a round bottom flask equipped with a stir bar and basified to pH = 7 with aq. NaOH (6 M). The volume was reduced to 20 mL by concentration *in vacuo* at which point white solids had precipitated. The solids were collected by vacuum filtration to provide (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 1-9**, 1.041 g, 3.24 mmol, 68%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.70 (s, 1H), 6.69 (s, 1H), 6.45 (s, 1H), 4.58 (d, J = 4.9 Hz, 1H), 3.72 (s, 3H), 3.32-3.25 (m, 2H), 2.98 (br d, J = 11.0 Hz, 1H), 2.90-2.77 (m, 3H), 2.47-2.42 (m, 2H), 2.32-2.26 (m, 1H), 2.02 (t, J = 10.4 Hz, 1H), 1.23 (q, J = 11.6 Hz, 1H), 1.17 (s, 9H).

EXAMPLE 3: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (Compound 1-9, see also International Application No. PCT/US2023/033206).

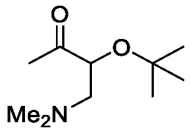


Step 1: Preparation of 1-(*tert*-butoxy)propan-2-one (Compound 1-20).



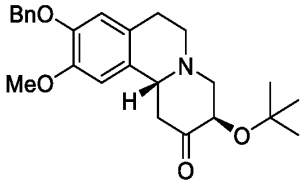
A solution of 4-(*tert*-butoxy)-3-oxobutanoic acid (**Compound 1-2**, 83.8 g, 481 mmol) in DMSO (166 mL) was heated with stirring at 45°C for 20h. The mixture was subjected to vacuum distillation to give 1-(*tert*-butoxy)propan-2-one (**Compound 1-20**, 55.1 g, 423 mmol, 88%) as a clear colorless oil with a boiling point of 50°C at 12 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.96 (s, 2H), 2.20 (s, 3H), 1.25 (s, 9H).

Step 2: Preparation of 3-(*tert*-butoxy)-4-(dimethylamino)butan-2-one (Compound 1-21).



To a solution of 1-(*tert*-butoxy)propan-2-one (**Compound 1-20**, 55.1 g, 423.3 mmol, 1.0 eq) in EtOH (275 mL) was added dimethylamine hydrochloride (51.8 g, 635 mmol, 1.5 eq), paraformaldehyde (25.4 g, 847 mmol, 2.0 eq) and aq. HCl (12.1 N, 1.75 mL, 21.2 mmol, 0.05 eq) and the mixture was stirred at 75°C for 22h. The mixture was cooled to RT, diluted with water, basified to pH = 12 with aq. NaOH (1M) and extracted five times with MTBE. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was split and submitted to two separate separations: a silica gel column (330 g) loaded using DCM run with an increasing gradient of MeOH (0-10% over 20 min) in DCM and a silica gel column (220 g) loaded using DCM run with an increasing gradient of MeOH (0-10% over 20 min) in DCM to give 3-(*tert*-butoxy)-4-(dimethylamino)butan-2-one (**Compound 1-21**, 25.1 g, 83% purity (w/w), 111 mmol, 26%) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.94 (t, J = 6.6 Hz, 1H), 2.45-2.35 (m, 2H), 2.13 (s, 6H), 2.08 (s, 3H), 1.10 (s, 9H).

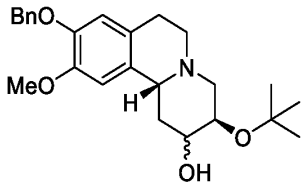
Step 3: Preparation of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (Compound (±)-1-5).



To a solution of 3-(*tert*-butoxy)-4-(dimethylamino)butan-2-one (**Compound 1-21**, 25.1 g, 83% purity (w/w), 111 mmol, 1.2 eq) in MeOH (110 mL) and water (58 mL) was added 6-(benzyloxy)-7-methoxy-3,4-dihydroisoquinoline hydrochloride (CAS Registry Number: 68360-23-6; **Compound 1-3**, 28.3 g, 93.0 mmol, 1.0 eq), sodium acetate (9.27 g, 113 mmol, 1.2 eq) and acetic acid (6.5 mL, 113 mmol, 1.2 eq). The mixture was stirred 40h at 45°C at which point a precipitate was formed. The mixture was cooled to room temperature and the precipitate was filtered. The solids were rinsed with 50% (v/v) MeOH in water (200 mL) and dried *in vacuo* for 16h to give (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (**Compound (±)-1-5**, 20.6 g, 50.3 mmol, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.46-7.31 (m, 5H), 6.81

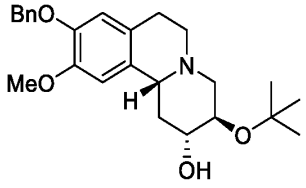
(s, 1H), 6.75 (s, 1H), 5.03 (s, 2H), 4.37 (dd, J = 7.0, 10.9 Hz, 1H), 3.74 (s, 3H), 3.46 (br d, J = 11.9 Hz, 1H), 3.23-3.09 (m, 2H), 2.95-2.84 (m, 2H), 2.70-2.62 (m, 1H), 2.59-2.42 (m, 3H), 1.15 (s, 9H).

Step 4: Preparation of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-*2H*-pyrido[2,1-*a*]isoquinolin-2-ol (Compound (±)-1-6).



To a solution of 9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (**Compound (±)-1-5**, 20.6 g, 50.3 mmol, 1.0 eq) in THF (200 mL) at 0°C was added DIBAL-H (1.0 M in hexanes, 75.4 mL, 75.4 mmol, 1.5 eq) dropwise. The mixture was stirred 2h at 0°C. The mixture was warmed to RT then an additional DIBAL-H (1.0 M in hexanes, 25.1 mL, 25.1 mmol, 0.5 eq) was added dropwise. The mixture was stirred 16h at RT. The reaction mixture was cooled to 0°C then quenched with acetone. The mixture was warmed to RT, diluted with DCM (200 mL) and aq. Rochelle's salt (10% w/w) and stirred vigorously until the emulsion dissipated. The mixture was extracted three times with MTBE. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol as a mixture of diastereomers (**Compound (±)-1-6**, 20.5 g, 49.8 mmol, 99%) that was carried on directly to the next step (synthesis of **Compound 1-8**).

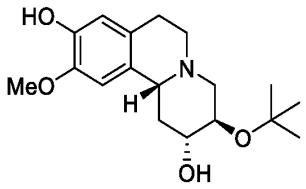
Step 5: Preparation of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (Compound 1-8).



To a solution of crude (±)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound (±)-1-6**, 20.5 g, 49.8 mmol, 1.0 eq) in EtOH (440 mL) was added (2*S*,3*S*)-2,3-bis(4-methylbenzoyloxy)butanedioic acid (DPTTA, 19.2 g, 49.8 mmol, 1.0 eq). The solution was heated to reflux with stirring which became a suspension upon further heating. After the addition of MeOH (150 mL) the mixture was held at reflux until a clear solution was obtained. The solution was cooled to 75°C, then seeded with **Compound 1-8·DPTTA** (0.070 g, see **EXAMPLE 1**) and held at constant temperature for 30 min. The mixture was cooled at a rate of 8°C per h to RT, then continued stirring for 16h. The resulting precipitate was collected by vacuum filtration, washed with MTBE (100 mL) and EtOH (40 mL), and dried *in vacuo* for 16h to

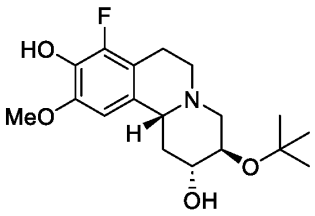
provide **Compound 1-8·DPTTA** (16.1 g, 20.1 mmol, 40% from **Compound (±)-1-5**) as a white solid. An optical purity of 100% ee was determined by chiral supercritical fluid chromatography (SFC) analysis and a diastereomeric purity ≥ 99%. The chiral salt pair was suspended in DCM and water was added. The mixture was basified with saturated aq. NH_4OH until pH ~ 10. The mixture was extracted three times with DCM. The organic extracts were dried over MgSO4, filtered, and concentrated *in vacuo* to afford (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound 1-8**, 8.13 g, 19.8 mmol, 39% from **Compound (±)-1-5**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.45-7.41 (m, 2H), 7.41-7.37 (m, 2H), 7.34-7.31 (m, 1H), 6.77 (s, 1H), 6.74 (s, 1H), 5.01 (s, 2H), 4.61 (d, J = 4.7 Hz, 1H), 3.73 (s, 3H), 3.32-3.27 (m, 2H), 3.02 (br d, J = 11.0 Hz, 1H), 2.92-2.82 (m, 3H), 2.54-2.45 (m, 2H), 2.35-2.29 (m, 1H), 2.04 (br t, J = 10.3 Hz, 1H), 1.27-1.21 (m, 1H), 1.17 (s, 9H).

Step 6: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (Compound 1-9).

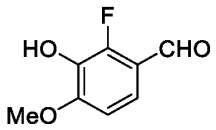


To a solution of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound 1-8**, 8.13 g, 19.8 mmol, 1.0 eq) in 3:1 MeOH:H_2O (42 mL) was added aq. HCl (12.1 M, 1.97 mL, 23.8 mmol, 1.2 eq) dropwise at 0°C with stirring. The mixture was stirred 10 min. Palladium on carbon (10% w/w, 1.06 g, 0.994 mmol, 0.05 eq) and ammonium formate (12.5 g, 198 mmol, 10 eq) were added and mixture was stirred at 50°C for 30 min. The mixture was cooled to 0°C and acidified to pH = 1 with aq. HCl (12.1 M). The suspension was filtered, and solids rinsed with MeOH. The filtrate was transferred to a round bottom flask equipped with a stir bar and basified to pH = 8 with aq. NaOH (6 M) at which point white solids had precipitated. The solids were collected by vacuum filtration and dried *in vacuo* 16h to provide (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 1-9**, 5.74 g, 17.9 mmol, 90%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.70 (s, 1H), 6.69 (s, 1H), 6.45 (s, 1H), 4.58 (d, J = 4.9 Hz, 1H), 3.72 (s, 3H), 3.32-3.25 (m, 2H), 2.98 (br d, J = 11.0 Hz, 1H), 2.90-2.77 (m, 3H), 2.47-2.42 (m, 2H), 2.32-2.26 (m, 1H), 2.02 (t, J = 10.4 Hz, 1H), 1.23 (q, J = 11.6 Hz, 1H), 1.17 (s, 9H).

EXAMPLE 4: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (Compound 2-11).

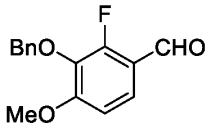


Step 1: Preparation of 2-fluoro-3-hydroxy-4-methoxybenzaldehyde (Compound 2-2).



To a solution of hexamethylenetetramine (203.38 g, 1.45 mol, 2.06 eq) in TFA (600 mL) was added a solution of 2-fluoro-6-methoxyphenol (**Compound 2-1**, 100 g, 703.59 mmol, 1 eq) in TFA (600 mL) dropwise at 80°C over the course of 1 h. The mixture was stirred at 80°C for 1h. Nine additional vials were set up as described above. All ten reaction mixtures were combined for work-up. The mixture was cooled to RT then concentrated *in vacuo*, then diluted with water (9.6 L). The aqueous layer was adjusted to pH = 7 with solid potassium carbonate at which point a precipitate was formed. The resulting precipitate was collected by vacuum filtration and dried to afford 2-fluoro-3-hydroxy-4-methoxybenzaldehyde (**Compound 2-2**, 340 g, 2.00 mol, 26%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.03 (s, 1H), 9.67 (s, 1H), 7.31 (dd, J = 8.6, 7.5 Hz, 1H), 6.99 (dd, J = 8.76, 1.0 Hz, 1H), 3.90 (s, 3H).

Step 2: Preparation of 3-(benzyloxy)-2-fluoro-4-methoxybenzaldehyde (Compound 2-3).



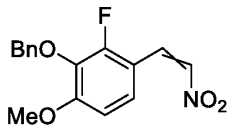
(Method A)

To a solution of 2-fluoro-3-hydroxy-4-methoxybenzaldehyde (**Compound 2-2**, 170 g, 899.27 mmol, 1 eq) in ACN (1.5 L) was added BnBr (benzyl bromide, 123.04 g, 719.42 mmol, 85.45 mL, 0.8 eq) and K_2CO_3 (372.87 g, 2.70 mol, 3 eq) and the mixture was stirred at 60°C for 2 h. One additional vial was set up as described above. All two reaction mixtures were combined for work-up. The mixture was cooled to RT, concentrated *in vacuo*, suspended in water (2 L) and extracted four times with ethyl acetate. The combined organic extracts were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 3-(benzyloxy)-2-fluoro-4-methoxybenzaldehyde (**Compound 2-3**, 400 g, 1.54 mol, 68%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.19 (s, 1H), 7.60 (dd, J = 8.6, 7.6 Hz, 1H), 7.47 (br d, J = 6.9 Hz, 2H), 7.35-7.40 (m, 3H), 6.80 (d, J = 9.0 Hz, 1H), 5.13 (s, 2H), 3.95 (s, 3H).

(Method B)

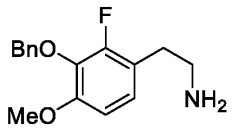
To a solution of 2-fluoro-3-hydroxy-4-methoxybenzaldehyde (**Compound 2-2**, 12.1 g, 71.12 mmol, 1 eq) in DMF (230 mL) was added BnBr (benzyl bromide, 18.25 g, 106.68 mmol, 12.67 mL, 1.5 eq) and K_2CO_3 (29.49 g, 213.36 mol, 3 eq) and the mixture was stirred at 60°C for 12 h. One additional vial (8.5 g) was set up as described above. All two reaction mixtures were combined for work-up. The mixture was cooled to RT, diluted with water (2 L) and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. A silica gel column was loaded and run with increasing gradient of EtOAc (0-20%) in hexanes to afford 3-(benzyloxy)-2-fluoro-4-methoxybenzaldehyde (**Compound 2-3**, 400 g, 1.54 mol, 68%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.19 (s, 1H), 7.60 (dd, J = 8.6, 7.6 Hz, 1H), 7.47 (br d, J = 6.9 Hz, 2H), 7.35-7.40 (m, 3H), 6.80 (d, J = 9.0 Hz, 1H), 5.13 (s, 2H), 3.95 (s, 3H),

Step 3: Preparation of 2-(benzyloxy)-3-fluoro-1-methoxy-4-(2-nitrovinyl) benzene (Compound 2-4).



To a solution of 3-(benzyloxy)-2-fluoro-4-methoxybenzaldehyde (**Compound 2-3**, 200 g, 614.77 mmol, 1 eq) in AcOH (1.5 mL) was added CH_3NO_2 (452.31 g, 7.41 mol, 401.34 mL, 12.05 eq) and NH_4OAc (161.12 g, 2.09 mol, 3.4 eq) and the mixture was stirred at 120°C for 4 h. One additional vial was set up as described above. All two reaction mixtures were combined for work-up. The mixture was cooled to RT, concentrated *in vacuo*, suspended in water (2 L) and extracted three times with DCM. The combined organic extracts were washed two times with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. A silica gel column was loaded and run with increasing gradient of EtOAc (0-10%) in hexanes to afford 2-(benzyloxy)-3-fluoro-1-methoxy-4-(2-nitrovinyl) benzene (**Compound 2-4**, 330 g, 1.09 mol, 68%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 13.8 Hz, 1H), 7.67 (d, J = 13.6 Hz, 1H), 7.46 (br d, J = 6.6 Hz, 2H), 7.35-7.39 (m, 3H), 7.20 (t, J = 8.2 Hz, 1H), 6.8 (dd, J = 8.9, 1.2 Hz, 1H), 5.12 (s, 2H), 3.94 (s, 3H),

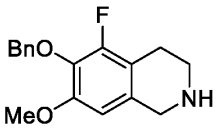
Step 4: Preparation of 2-(3-(benzyloxy)-2-fluoro-4-methoxyphenyl) ethan-1-amine (Compound 2-5).



To a solution of 2-(benzyloxy)-3-fluoro-1-methoxy-4-(2-nitrovinyl) benzene (**Compound 2-4**, 66 g, 167.97 mmol, 1 eq) in THF (330 mL) at 0 °C was added BH_3·THF (1 M, 839.86 mL, 5 eq). The mixture was heated at 70 °C with stirring for 12 h. Four additional vials were set up as described above. All five reaction mixtures were combined for work-up. The mixture was cooled to 0°C and

added aq. HCl (6 M, 2.5 L) slowly, the mixture was diluted with water (1 L) and stirred at RT for 2 h. The mixture was washed three times with methyl tert-butyl ether. The aqueous solution was cooled with an ice water bath and slowly treated with aq. NaOH (10 M, 1.6 L), the mixture was extracted three times with 2-methyltetrahydrofuran, the combined organic extracts was washed two times with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 2-(3-(benzyloxy)-2-fluoro-4-methoxyphenyl) ethan-1-amine (**Compound 2-5**, 200 g, 0.72 mol, 72%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (br d, J = 6.7 Hz, 2H), 7.31-7.39 (m, 3H), 6.84 (t, J = 8.2 Hz, 1H), 6.64 (dd, J = 8.5, 1.5 Hz, 1H), 5.09 (s, 2H), 3.85 (s, 3H), 2.86-2.94 (m, 2H), 2.67-2.75 (m, 2H).

Step 5: Preparation of 6-(benzyloxy)-5-fluoro-7-methoxy-1,2,3,4-tetrahydroisoquinoline (Compound 2-6).



To a solution of 2-(3-(benzyloxy)-2-fluoro-4-methoxyphenyl) ethan-1-amine (**Compound 2-5**, 155 g, 467.28 mmol, 1 eq) in HCOOH (1.5 L) was added paraformaldehyde (18.24 g, 607.46 mmol, 1.3 eq) and the mixture was stirred at 40°C for 12 h. The mixture was cooled to RT, concentrated *in vacuo*, suspended in water (500 mL), and basified to pH = 11 by with aq. NaOH (3.75 M), at which point a gelatinous compound was formed. Then ethyl acetate (80 mL) was added, and the gelatinous compound was converted to solid. The resulting precipitate was collected by vacuum filtration, washed with EtOAc, and dried *in vacuo* to afford 6-(benzyloxy)-5-fluoro-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**Compound 2-6**, 80 g, 0.28 mol, 54%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.29-7.48 (m, 5H), 6.66 (s, 1H), 4.97 (s, 2H), 3.77 (s, 3H), 3.60 (br s, 2H), 3.21 (s, 1H), 2.60-2.81 (m, 4H).

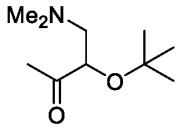
Step 6: Preparation of 6-(benzyloxy)-5-fluoro-7-methoxy-3,4-dihydroisoquinoline (Compound 2-7).



To a solution of 6-(benzyloxy)-5-fluoro-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**Compound 2-6**, 80 g, 250.58 mmol, 1 eq) in CH_3COOH (640 mL) was added hexamethylenetetramine (23.93 g, 170.70 mmol, 0.681 eq) and TFA (160 mL). The mixture was stirred at 90°C for 2 h. The mixture was cooled to RT, concentrated *in vacuo*, then diluted with water (600 mL). The aqueous layer was adjusted to pH = 11 with aq. NaOH (3.75 M), extracted three times with dichloromethane, the combined organic extracts were washed two times with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford 6-(benzyloxy)-5-fluoro-7-methoxy-3,4-dihydroisoquinoline (**Compound 2-7**, 33 g, 0.12 mol, 46%) as

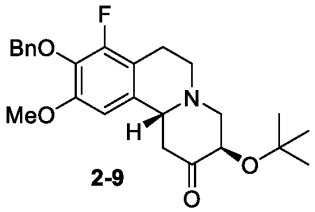
a light yellow solid. Obs. Ion (m/z) = 286.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.26 (br s, 1H), 7.48 (d, J = 6.9 Hz, 2H), 7.29-7.42 (m, 3H), 6.68 (s, 1H), 5.15 (s, 2H), 3.89 (s, 3H), 3.72-3.80 (m, 2H), 2.71 (t, J = 7.9 Hz, 2H).

Step 7: Preparation of 3-(*tert*-butoxy)-4-(dimethylamino)butan-2-one (Compound 2-8).



To a solution of 1-(*tert*-butoxy)propan-2-one (**Compound 1-20**, 55.1 g, 423.3 mmol, 1.0 eq) in EtOH (275 mL) was added dimethylamine hydrochloride (51.8 g, 635 mmol, 1.5 eq), paraformaldehyde (25.4 g, 847 mmol, 2.0 eq) and aq. HCl (12.1 N, 1.75 mL, 21.2 mmol, 0.05 eq) and the mixture was stirred at 75°C for 22h. The mixture was cooled to RT, diluted with water, basified to pH = 12 with aq. NaOH (1M) and extracted five times with MTBE. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was split and submitted to two separate separations: a silica gel column (330 g) loaded using DCM run with an increasing gradient of MeOH (0-10% over 20 min) in DCM and a silica gel column (220 g) loaded using DCM run with an increasing gradient of MeOH (0-10% over 20 min) in DCM to give 3-(*tert*-butoxy)-4-(dimethylamino)butan-2-one (**Compound 2-8**, 25.1 g, 83% purity (w/w), 111 mmol, 26%) as an oil. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.94 (t, J = 6.6 Hz, 1H), 2.45-2.35 (m, 2H), 2.13 (s, 6H), 2.08 (s, 3H), 1.10 (s, 9H).

Step 8: Preparation of (±)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*α*]isoquinolin-2-one (Compound 2-9).

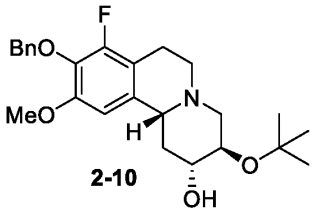


2-9

To a solution of 3-(*tert*-butoxy)-4-(dimethylamino)butan-2-one (**Compound 2-8**, 0.573 g, 3.06 mmol, 1.2 eq.) in MeOH (3 mL) was added 6-(benzyloxy)-5-fluoro-7-methoxy-3,4-dihydroisoquinoline (**Compound 2-7**, 0.727 g, 2.55 mmol, 1.0 eq). A solution of NaOAc (0.255 g, 3.11 mmol, 1.22 eq) and AcOH (0.178 mL, 3.11 mmol, 1.22 eq) in water (1.5 mL) was added and the mixture was stirred at 65°C for 3d. The mixture was cooled to RT and diluted with water. The aqueous layer was extracted three times with DCM. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A silica gel column (24 g) was loaded and run with an increasing gradient of 20% MeOH in DCM with 1% conc. NH_4OH (0-50% over 35 min) in DCM to afford (±)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*α*]isoquinolin-2-one (**Compound 2-9**, 1.08 g, 2.55 mmol, 99%) as a brown oil. Obs. Ion

(m/z) = 428.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.46-7.29 (m, 5H), 6.73 (s, 1H), 4.99 (s, 2H), 4.37 (dd, J = 6.9, 10.9 Hz, 1H), 3.82 (s, 3H), 3.50 (br d, J = 10.0 Hz, 1H), 3.23-3.09 (m, 2H), 2.94 (dd, J = 2.9, 13.6 Hz, 1H), 2.77-2.66 (m, 2H), 2.61-2.52 (m, 2H), 2.48-2.41 (m, 1H), 1.14 (s, 9H).

Step 9: Preparation of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (Compound 2-10).



2-10

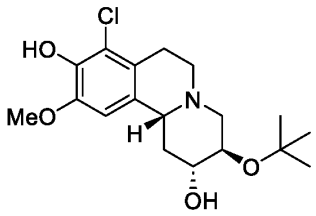
To a solution of (±)-(3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (**Compound 2-9**, 33 g, 77 mmol, 1.0 eq) in THF (700 mL) was added DIBAL-H (116 mL, 1 M in hexane, 116 mmol, 1.5 eq) dropwise at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature. After stirring at room temperature for another 1 h, the reaction mixture was quenched with potassium sodium tartrate (sat. in water, 700 mL) carefully. After stirring at room temperature for 16 h, the two phases were separated. The aqueous phase was extracted three times with ethyl acetate. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by two silica gel columns (2 × 220 g) was loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 25 min) in hexanes to afford racemic product. The racemic mixture was separated by supercritical fluid chromatography (OJ-H column, 2 × 25 cm) loaded using methanol and run with 15% methanol (0.1% DEA)/CO_2 (100 bar, 70 mL/min, 220 nm) to afford (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound 2-10**, 6.1 g, 14 mmol, 18% yield) as a white solid. Ion (m/z) = 430.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.40-7.47 (m, 2H), 7.27-7.40 (m, 3H), 6.73 (s, 1H), 4.98 (s, 2H), 4.63 (d, J = 4.6 Hz, 1H), 3.81 (s, 3H), 3.32 (br s, 1H), 3.05 (br d, J = 11.1 Hz, 1H), 2.87-2.98 (m, 2H), 2.62-2.74 (m, 1H), 2.55-2.62 (m, 1H), 2.53 (br d, J = 3.4 Hz, 1H), 2.30 (td, J = 11.1, 4.2 Hz, 1H), 2.05 (br t, J = 10.4 Hz, 1H), 1.21-1.35 (m, 1H), 1.18-1.21 (m, 1H), 1.17 (s, 9H). ^{19}F NMR (376 MHz, DMSO-d_6): δ = -136.20 (s).

Step 10: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (Compound 2-11).

To a solution of (2*R*,3*R*,11b*R*)-9-(benzyloxy)-3-(tert-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol (**Compound 2-10**, 0.67 g, 1.56 mmol, 1.0 eq) in 3:1 MeOH·H_2O (3.5 mL) was added aq. HCl (12.1 M, 0.18 mL, 1.87 mmol, 1.2 eq) dropwise at 0°C with stirring. The mixture was stirred 10 min. Palladium on carbon (10% w/w, 0.083 g, 0.078

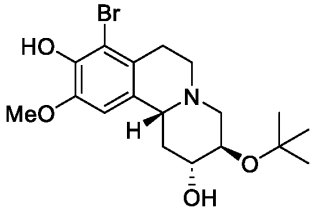
mmol, 0.05 eq) and ammonium formate (0.984 g, 15.6 mmol, 10 eq) were added and mixture was stirred at 50°C for 30 min. The mixture was cooled to 0°C and acidified to pH = 1 with aq. HCl (12.1 M). The suspension was filtered, and solids rinsed with water and aq. HCl (12.1 M). The filtrate was transferred to a round bottom flask equipped with a stir bar and basified to pH = 8 with aq. NaOH (6 M) at which point white solids had precipitated. The mixture was stirred at RT for 1 h. The solids were collected by vacuum filtration to provide (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinoline-2,9-diol (**Compound 2-11**, 0.468 g, 1.378 mmol, 88%) as a white solid. Obs. Ion (m/z) = 340.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.61 (s, 1H), 4.60 (d, J = 4.4 Hz, 1H), 3.76 (s, 3H), 3.31-3.26 (m, 2H), 2.99 (br d, J = 11.0 Hz, 1H), 2.95-2.87 (m, 2H), 2.74-2.61 (m, 1H), 2.61-2.41 (m, 2H), 2.35-2.22 (m, 1H), 2.03 (br t, J = 10.5 Hz, 1H), 1.29-1.19 (m, 1H), 1.17 (s, 9H).

EXAMPLE 5: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (Compound 3-1).



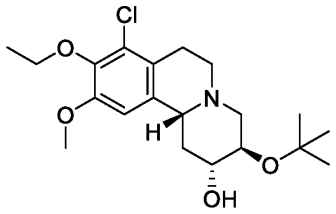
To a suspension of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 1-9**, 1.2 g, 3.7 mmol, 1.0 eq) in water (12 mL) was added sulfuric acid (18.3M, 0.20 mL, 3.7 mmol, 1.0 eq) at room temperature. The mixture was then added *N*-chlorosuccinimide (NCS, 1.0 g, 7.5 mmol, 2.0 eq) in one portion at room temperature. After stirring at room temperature for 16 h, the reaction mixture was quenched with $NaHCO_3$ (sat. in H_2O) and extracted five times with DCM. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (20 g) loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 20 min) in hexanes, followed by a HP C_{18} reverse phase column (100 g) loaded using DMSO and run with an increasing gradient of MeCN (10-50% over 20 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 3-1**, 0.75 g, 2.1 mmol, 56% yield) as a white solid. Obs. Ion (m/z) = 356.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.11 (br d, J = 2.6 Hz, 1H), 6.79 (s, 1H), 4.60 (br d, J = 4.2 Hz, 1H), 3.79 (s, 3H), 3.19-3.28 (m, 1H), 3.01 (br d, J = 11.1 Hz, 1H), 2.86-2.97 (m, 2H), 2.64-2.73 (m, 1H), 2.56-2.64 (m, 1H), 2.47 (br s, 1H), 2.30 (td, J = 11.1, 4.5 Hz, 1H), 2.03 (br t, J = 10.3 Hz, 1H), 1.20-1.28 (m, 1H), 1.18-1.20 (m, 1H), 1.17 (s, 9H).

EXAMPLE 6: Preparation of (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (Compound 3-2).



To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 1-9**, 2.25 g, 7.00 mmol, 1.0 eq) in H_2SO_4 (0.1 M in H_2O, 35 mL, 3.5 mmol, 0.5 eq) added *N*-bromosuccinimide (NBS, 1.87 g, 10.5 mmol, 1.5 eq) in one portion at room temperature. After stirring at room temperature for 4 h, the reaction mixture was added another batch of *N*-bromosuccinimide (1.25 g, 7 mmol, 1 eq). After stirring at room temperature for 16 h, the reaction mixture was quenched with $NaHCO_3$ (sat. in H_2O) and extracted three times with 20% *i*PrOH in DCM. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (20 g) loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 20 min) in hexanes, followed by a HP C_{18} reverse phase column (100 g) loaded using DMSO and run with an increasing gradient of MeCN (10-75% over 20 min) in H_2O to afford (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 3-2**, 1.16 g, 2.88 mmol, 41% yield) as a light brown solid. Obs. Ion (m/z) = 400.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.18 (br d, J = 0.9 Hz, 1H), 6.83 (s, 1H), 4.60 (br d, J = 4.2 Hz, 1H), 3.80 (s, 3H), 3.26-3.29 (m, 1H), 3.03 (br d, J = 11.0 Hz, 1H), 2.83-2.98 (m, 2H), 2.62-2.73 (m, 1H), 2.54-2.61 (m, 1H), 2.42-2.48 (m, 1H), 2.30 (td, J = 11.1, 4.2 Hz, 1H), 2.03 (br t, J = 10.3 Hz, 1H), 1.21-1.30 (m, 1H), 1.18-1.21 (m, 1H), 1.17 (s, 9H).

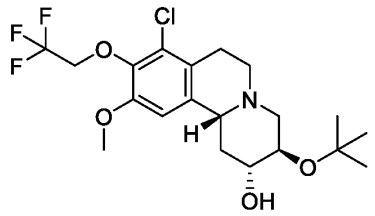
EXAMPLE 7: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 89).



To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 3-1**, 0.20 g, 0.56 mmol, 1.0 eq) in DMF (6 mL) was added Cs_2CO_3 (0.55 g, 1.7 mmol, 3.0 eq) and iodoethane (83 mg, 0.53 mmol, 0.95 eq) at room temperature. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted five times with DCM. The combined organic layer was dried over

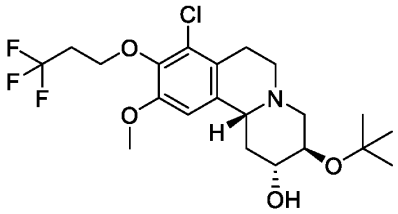
Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (4 g) loaded using DCM and run with an increasing gradient of EtOAc (0-80% over 20 min) in hexanes, followed by a HP C_{18} reverse phase column (20 g) loaded using DMSO and run with an increasing gradient of MeCN (5-70% over 20 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 89**, 0.12 g, 0.32 mmol, 56% yield) as a white solid. Obs. Ion (m/z) = 384.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.88 (s, 1H), 4.64 (d, J = 4.5 Hz, 1H), 3.95 (q, J = 7.0 Hz, 2H), 3.80 (s, 3H), 3.28-3.30 (m, 1H), 3.07 (br d, J = 10.9 Hz, 1H), 2.87-3.00 (m, 2H), 2.66-2.76 (m, 1H), 2.58-2.66 (m, 1H), 2.53 (br d, J = 2.7 Hz, 1H), 2.32 (td, J = 11.0, 4.6 Hz, 1H), 2.05 (br t, J = 10.5 Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H), 1.24 (br s, 1H), 1.18-1.20 (m, 1H) 1.17 (s, 9H).

EXAMPLE 8: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 96).



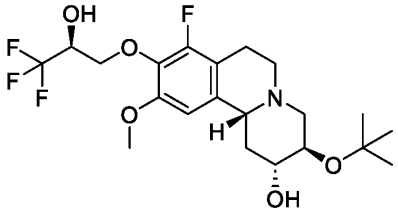
To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 3-1**, 0.13 g, 0.36 mmol, 1.0 eq) in DMF (5 mL) was added Cs_2CO_3 (0.36 g, 1.1 mmol, 3.0 eq) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.127 g, 0.55 mmol, 1.5 eq) at room temperature. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted five times with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (12 g) loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 15 min) in hexanes, followed by a HP C_{18} reverse phase column (30 g) loaded using DMSO and run with an increasing gradient of MeCN (5-60% over 20 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 96**, 0.109 g, 0.25 mmol, 68% yield) as a white solid. Obs. Ion (m/z) = 438.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.96 (s, 1H), 4.65 (d, J = 4.6 Hz, 1H), 4.57 (q, J = 9.1 Hz, 2H), 3.84 (s, 3H), 3.28 (br s, 1H), 3.09 (br d, J = 11.2 Hz, 1H), 2.89-3.01 (m, 2H), 2.63-2.75 (m, 2H), 2.54-2.63 (m, 1H), 2.28-2.37 (m, 1H), 2.01-2.11 (m, 1H), 1.25 (br d, J = 11.6 Hz, 1H), 1.18-1.21 (m, 1H), 1.17 (s, 9H).

EXAMPLE 9: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 97).



To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 3-1**, 0.11 g, 0.31 mmol, 1.0 eq) in DMF (5 mL) was added Cs_2CO_3 (0.30 g, 0.93 mmol, 3.0 eq) and 3,3,3-trifluoropropyl trifluoromethanesulfonate (0.091 g, 0.37 mmol, 1.2 eq) at room temperature. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted five times with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (12 g) loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 10 min) in hexanes, followed by a HP C_{18} reverse phase column (30 g) loaded using DMSO and run with an increasing gradient of MeCN (5-60% over 30 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 97**, 0.083 g, 0.18 mmol, 60% yield) as a white solid. Obs. Ion (m/z) = 452.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.92 (s, 1H), 4.64 (d, J = 4.6 Hz, 1H), 4.09 (t, J = 6.1 Hz, 2H), 3.81 (s, 3H), 3.07 (br d, J = 10.5 Hz, 1H), 2.95-3.00 (m, 1H), 2.92 (dd, J = 11.4, 3.3 Hz, 1H), 2.59-2.80 (m, 5H), 2.53 (br d, J = 2.2 Hz, 1H), 2.28-2.36 (m, 1H), 1.99-2.10 (m, 1H), 1.22-1.31 (m, 1H), 1.19-1.21 (m, 1H), 1.17 (s, 9H).

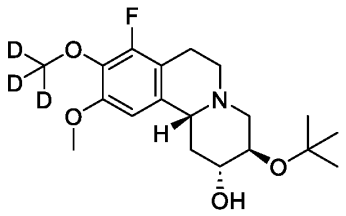
EXAMPLE 10: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 30).



To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 2-11**, 50.9 mg, 0.15 mmol, 1.0 eq) in DMF (1.5 mL) was added Cs_2CO_3 (0.15 g, 0.45 mmol, 3.0 eq) and (*S*)-(−)-3,3,3-trifluoro-1,2-epoxypropane (16.8 mg, 0.15 mmol, 1.0 eq) at 0 °C. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted five times with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (4 g) loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 15 min) in

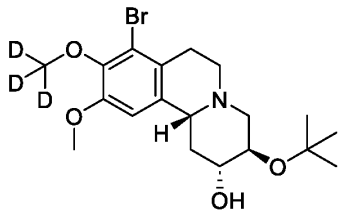
hexanes, followed by a HP C_{18} reverse phase column (15.5 g) loaded using DMSO and run with an increasing gradient of MeCN (5-60% over 30 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 30**, 35.1 mg, 0.078 mmol, 52% yield) as a white solid. Obs. Ion (m/z) = 452.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.74 (s, 1H), 6.55 (d, J = 6.5 Hz, 1H), 4.64 (d, J = 4.3 Hz, 1H), 4.21-4.34 (m, 1H), 4.06-4.15 (m, 1H), 3.96-4.04 (m, 1H), 3.80 (s, 3H), 3.24-3.29 (m, 1H), 3.05 (br d, J = 11.1 Hz, 1H), 2.85-2.98 (m, 2H), 2.63-2.76 (m, 1H), 2.55-2.63 (m, 1H), 2.53 (br s, 1H), 2.24-2.35 (m, 1H), 2.05 (br t, J = 10.3 Hz, 1H), 1.21-1.31 (m, 1H), 1.18-1.20 (m, 1H), 1.17 (s, 9H).

EXAMPLE 11: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-($^2H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 74).



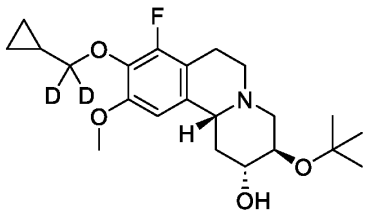
To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 2-11**, 50.9 mg, 0.15 mmol, 1.0 eq) in DMF (1.5 mL) was added Cs_2CO_3 (0.15 g, 0.45 mmol, 3.0 eq) and dimethyl sulfate-d_6 (19.8 mg, 0.15 mmol, 1.0 eq) at 0 °C. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted five times with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (4 g) loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 15 min) in hexanes, followed by a HP C_{18} reverse phase column (15.5 g) loaded using DMSO and run with an increasing gradient of MeCN (5-60% over 40 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-($^2H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 74**, 12.5 mg, 0.035 mmol, 23% yield) as a white solid. Obs. Ion (m/z) = 357.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.71 (s, 1H), 4.63 (d, J = 4.3 Hz, 1H), 3.79 (s, 3H), 3.23-3.29 (m, 1H), 3.04 (br d, J = 11.2 Hz, 1H), 2.86-2.97 (m, 2H), 2.62-2.74 (m, 1H), 2.55-2.62 (m, 1H), 2.51-2.54 (m, 1H), 2.29 (td, J = 11.2, 4.1 Hz, 1H), 2.05 (br t, J = 10.4 Hz, 1H), 1.22-1.33 (m, 1H), 1.19-1.22 (m, 1H), 1.17 (s, 9H).

EXAMPLE 12: Preparation of (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^2H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 166).



To a solution of (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 3-2**, 60.0 mg, 0.15 mmol, 1.0 eq) in DMF (1.5 mL) was added Cs_2CO_3 (0.15 g, 0.45 mmol, 3.0 eq) and dimethyl sulfate-d_6 (19.8 mg, 0.15 mmol, 1.0 eq) at 0 °C. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted five times with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (4 g) was loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 15 min) in hexanes, followed by a HP C_{18} reverse phase column (15.5 g) was loaded using DMSO and run with an increasing gradient of MeCN (5-70% over 20 min) in H_2O to afford (2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^2H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 166**, 41.3 mg, 0.099 mmol, 66% yield) as a white solid. Obs. Ion (m/z) = 417.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.94 (s, 1H), 4.64 (d, J = 4.6 Hz, 1H), 3.81 (s, 3H), 3.32-3.41 (m, 1H), 3.08 (br d, J = 11.5 Hz, 1H), 2.87-3.00 (m, 2H), 2.63-2.73 (m, 1H), 2.56-2.62 (m, 1H), 2.54 (br s, 1H), 2.32 (td, J = 11.2, 4.5 Hz, 1H), 2.05 (br t, J = 10.4 Hz, 1H), 1.22-1.31 (m, 1H), 1.19-1.21 (m, 1H), 1.17 (s, 9H).

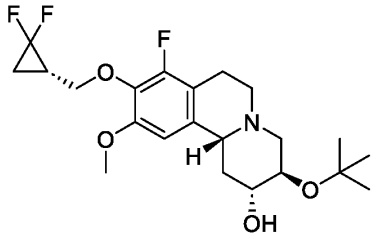
EXAMPLE 13: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 68).



To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 2-11**, 44 mg, 0.13 mmol, 1.0 eq) in DMF (0.6 mL) was added Cs_2CO_3 (0.13 g, 0.39 mmol, 3.0 eq) and (iodomethyl-d_2)cyclopropane (25 mg, 0.14 mmol, 1.2 eq) at 0 °C. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted five times with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (4 g) that was loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 15 min) in hexanes, followed by a HP C_{18} reverse phase column (15.5 g) loaded using DMSO and run with an increasing

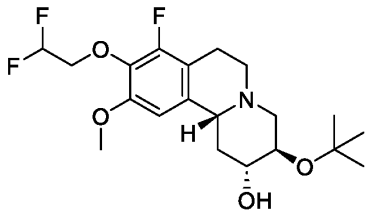
gradient of MeCN (5-70% over 20 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 68**, 33 mg, 0.082 mmol, 63% yield) as a white solid. Obs. Ion (m/z) = 396.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.68 (s, 1H), 4.63 (br s, 1H), 3.77 (s, 3H), 3.25-3.30 (m, 1H), 3.03 (br d, J = 11.0 Hz, 1H), 2.91 (br d, J = 10.3 Hz, 2H), 2.65 (br dd, J = 10.8, 5.4 Hz, 1H), 2.54-2.61 (m, 1H), 2.44-2.49 (m, 1H), 2.29 (td, J = 10.9, 3.8 Hz, 1H), 2.04 (br t, J = 10.1 Hz, 1H), 1.21-1.41 (m, 2H), 1.17 (s, 9H), 1.11 (br dd, J = 8.1, 3.9 Hz, 1H), 0.43-0.53 (m, 2H), 0.21 ppm (q, J = 4.8 Hz, 2H).

EXAMPLE 14: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 21).



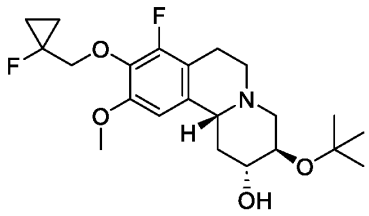
To a solution of (*S*)-(2,2-difluorocyclopropyl)methanol(0.025 ml, 0.294 mmol, 2.0 eq) in toluene (1.9 ml) was added 2-(tributyl-λ^5-phosphaneylidene)acetonitrile (0.077 ml, 0.294 mmol, 2.0 eq) and (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 2-11**, 0.05 g, 0.147 mmol, 1.0 eq). The mixture was stirred at 100 °C for 2h. The mixture was cooled to RT and concentrated *in vacuo*. The crude material was submitted to two chromatographic separations: two silica gel columns (4 g) were loaded using DCM run with an increasing gradient of EtOAc (0-100% over 30 min) in hexanes to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 21**, 0.039 g, 0.0903 mmol, 61%) as a white solid. Obs. Ion (m/z) = 430.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.72 (s, 1H), 4.63 (br d, J = 3.2 Hz, 1H), 4.10 (ddd, J = 10.7, 6.4, 3.7 Hz, 1H), 3.88 (t, J = 10.0 Hz, 1H), 3.79 (s, 3H), 3.31-3.25 (m, 2H), 3.04 (br d, J = 11.3 Hz, 1H), 2.97-2.87 (m, 2H), 2.74-2.51 (m, 3H), 2.29 (td, J = 11.2, 4.0 Hz, 1H), 2.16-2.00 (m, 2H), 1.63 (tdd, J = 12.0, 7.6, 4.8 Hz, 1H), 1.38-1.21 (m, 2H), 1.17 (s, 9H).

EXAMPLE 15: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 28).



To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 2-11**, 75 mg, 0.22 mmol, 1.0 eq) in DMF (0.75 mL) was added Cs_2CO_3 (0.216 g, 0.66 mmol, 3.0 eq) and 2,2-difluoroethyl trifluoromethanesulfonate (71 mg, 0.33 mmol, 1.5 eq) at 0 °C. After stirring at room temperature for 16 h, the reaction mixture was filtered through celite and loaded onto a HP C_{18} reverse phase column (15.5 g) that was run with an increasing gradient of MeCN (5-100% over 20 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 28**, 26 mg, 0.064 mmol, 29% yield) as a white solid. Obs. Ion (m/z) = 404.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.76 (bs, 1H), 6.27 (tt, J = 56.0, 4.0 Hz, 1H), 4.66 (d, J = 4.0 Hz, 1H), 4.20 (td, J = 14.9, 3.6 Hz, 2H), 3.82 (s, 3H), 3.27-3.35 (m, 2H), 3.06 (bd, J = 12.0 Hz, 1H), 2.91-2.95 (m, 2H), 2.54-2.74 (m, 3H), 2.26-2.35 (m, 1H), 2.02-2.09 (m, 1H), 1.22-1.31 (m, 1H), 1.18 (s, 9H).

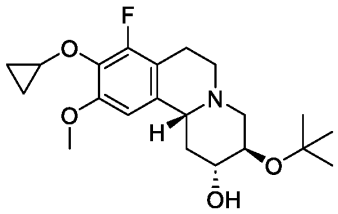
EXAMPLE 16: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 52).



To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 2-11**, 44 mg, 0.13 mmol, 1.0 eq) in DMF (0.6 mL) was added Cs_2CO_3 (0.13 g, 0.39 mmol, 3.0 eq) and 1-(bromomethyl)-1-fluorocyclopropane (21 mg, 0.14 mmol, 1.05 eq) at 0 °C. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted five times with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column (4 g) that was loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 15 min) in hexanes, followed by a HP C_{18} reverse phase column (15.5 g) that was loaded using DMSO and run with an increasing gradient of MeCN (5-70% over 20 min) in H_2O to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-

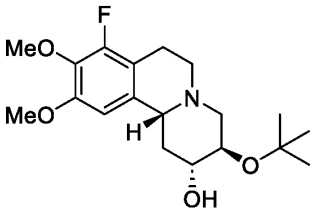
pyrido[2,1-a]isoquinolin-2-ol (**Compound 52**, 34 mg, 0.084 mmol, 65% yield) as a white solid. Obs. Ion (m/z) = 412.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.71 (s, 1H), 4.63 (br d, J = 3.9 Hz, 1H), 4.12-4.27 (m, 2H), 3.79 (s, 3H), 3.25-3.31 (m, 1H), 3.04 (br d, J = 11.0 Hz, 1H), 2.88-2.96 (m, 2H), 2.62-2.74 (m, 1H), 2.55-2.62 (m, 1H), 2.52 (br s, 1H), 2.30 (td, J = 11.1, 3.8 Hz, 1H), 2.05 (br t, J = 10.3 Hz, 1H), 1.19-1.43 (m, 2H), 1.17 (s, 9H), 0.99-1.10 (m, 2H), 0.77 ppm (q, J = 7.6 Hz, 2H).

EXAMPLE 17: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclopropoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 70).



To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 2-11**, 0.050 g, 0.147 mmol, 1.0 eq) in DMF (1.5 mL) was added cesium carbonate (0.144 g, 0.441 mmol, 3.0 eq) and the resulting mixture was stirred at RT for 10 min. Then, cyclopropyl trifluoromethanesulfonate (0.0352 mL, 0.294 mmol, 2.0 eq) was added and the mixture was stirred at RT overnight. The mixture was diluted with EtOAc and rinsed five times with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A silica gel column (4 g) was loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 30 min) in hexanes to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclopropoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 70**, 0.032 g, 0.0843 mmol, 57%) as a white solid. Obs. Ion (m/z) = 380.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.73 (s, 1H), 4.64 (d, J = 4.4 Hz, 1H), 4.06 (td, J = 5.8, 3.1 Hz, 1H), 3.79 (s, 3H), 3.26-3.30 (m, 1H), 3.05 (br d, J = 11.0 Hz, 1H), 2.89-2.97 (m, 2H), 2.63-2.74 (m, 1H), 2.51-2.63 (m, 2H), 2.30 (td, J = 11.2, 4.0 Hz, 1H), 2.05 (br t, J = 10.4 Hz, 1H), 1.21-1.34 (m, 1H), 1.17 (s, 9H), 0.67-0.74 (m, 2H), 0.47-0.54 ppm (m, 2H).

EXAMPLE 18: Preparation of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (Compound 34).



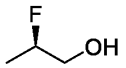
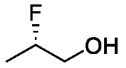
To a solution of (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,9-diol (**Compound 2-11**, 0.05 g, 0.147 mmol, 1.0 eq) in 9:1 MeCN:MeOH (2.2 ml) was added N,N-diisopropylethylamine (0.127 mL, 0.735 mmol, 5.0 eq) and trimethylsilyldiazomethane (2M, 0.367 mL, 0.735 mmol, 5.0 eq) and the resulting mixture was stirred at 60 °C overnight. The mixture was cooled to RT and quenched with AcOH (0.05 mL). The mixture was concentrated *in vacuo*. A silica gel column (4 g) was loaded using DCM and run with an increasing gradient of EtOAc (0-100% over 30 min) in hexanes to afford (2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 34**), 0.027 g, 0.0764 mmol, 52%) as a white solid. Obs. Ion (m/z) = 354.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.71 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.26-3.36 (m, 2H), 3.04 (br d, J = 11.3 Hz, 1H), 2.86-2.97 (m, 2H), 2.55-2.73 (m, 2H), 2.46-2.54 (m, 2H), 2.29 (td, J = 11.2, 4.2 Hz, 1H), 2.05 (br t, J = 10.4 Hz, 1H), 1.19-1.34 (m, 1H), 1.17 (s, 9H).

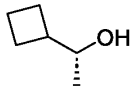
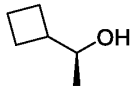
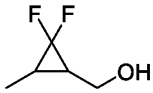
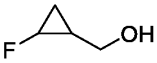
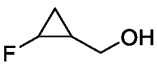
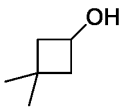
EXAMPLE 19: Reagents used in the preparation of certain compounds described in Table A, Table B, and Table C.

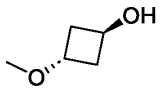
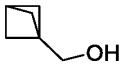
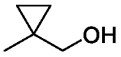
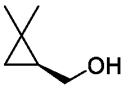
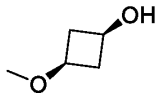
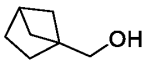
Additional compounds shown in **Table A**, **Table B**, and **Table C** were prepared using similar methods as described in the above examples and the following reagents shown in **Table 3**.

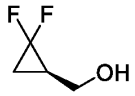
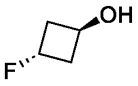
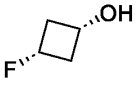
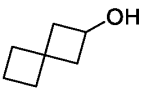
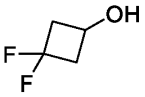
Table 3 also provides the observed (Obs) ion m/z ratio for the title compound.

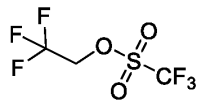
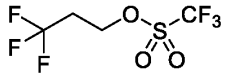
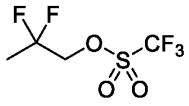
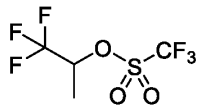
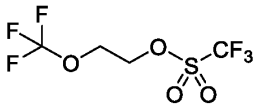
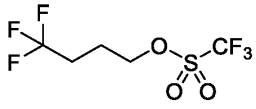
Table 3

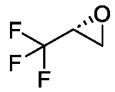
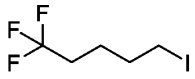
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
1		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*R*)-2-fluoropropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	400.3
2		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*S*)-2-fluoropropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	400.3

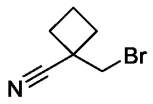
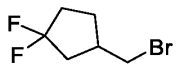
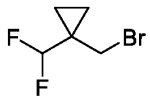
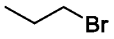
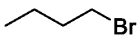
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
3		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(1*S*)-1-cyclobutylethoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	422.3
4		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(1*R*)-1-cyclobutylethoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	422.5
5 [1]		*trans*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluoro-3-methylcyclopropyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	444.3
6 [2]		*cis*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	412.3
7 [1]		*trans*-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	412.3
8		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(3,3-dimethylcyclobutoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	422.3

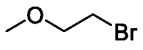
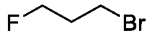
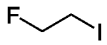
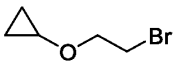
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
9		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-methoxycyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	424.3
10		(2*R*,3*R*,11b*R*)-9-{bicyclo[1.1.1]pentan-1-ylmethoxy}-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	420.3
11		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1-methylcyclopropyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	408.3
12		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-dimethylcyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	422.3
13		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-methoxycyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	424.3
14		(2*R*,3*R*,11b*R*)-9-{bicyclo[2.1.1]hexan-1-ylmethoxy}-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	434.3

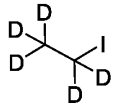
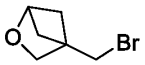
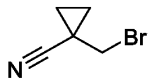
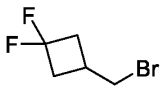
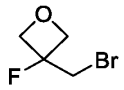
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
15		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(1-methylcyclobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	407.2
16		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*R*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	430.2
17		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-fluorocyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	412.3
18		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-fluorocyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	412.3
19		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-{spiro[3.3]heptan-2-yloxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	434.5
20		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(3,3-difluorocyclobutoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	429.2

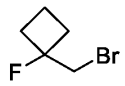
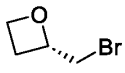
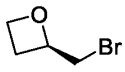
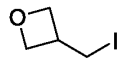
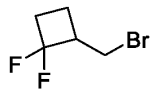
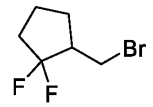
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
22		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	422.2
23		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	436.2
24		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	418.3
25		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1,1,1-trifluoropropan-2-yl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	436.2
26		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[2-(trifluoromethoxy)ethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	452.2
27		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(4,4,4-trifluorobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	450.2

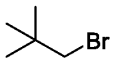
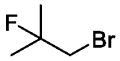
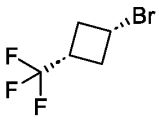
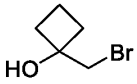
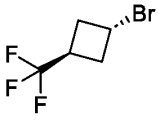
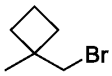
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
29		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	452.0
31		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	398.3
32		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	398.3
33		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-hydroxy-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	412.3
35		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	396.3
36		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	464.3

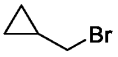
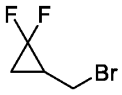
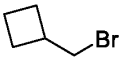
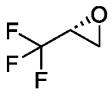
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
37		1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile	433.3
38		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclopentyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	458.3
39		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	444.3
40		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	382.3
41		(2*R*,3*R*,11b*R*)-9-butoxy-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	396.3
42		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	382.2

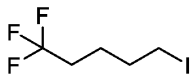
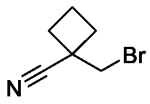
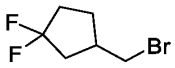
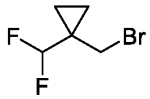
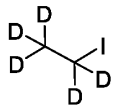
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
43		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	396.2
44		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	398.2
45		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(3-fluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	400.2
46		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-fluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	386.2
47		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2-cyclopropoxyethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	424.3
48		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclobutoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	394.3

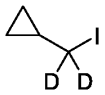
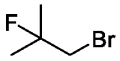
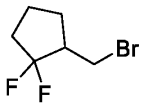
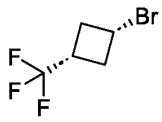
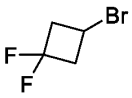
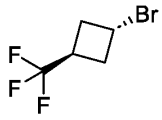
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
49		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-($^{2}H_5$)ethoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	373.2
50		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-{2-oxabicyclo[2.1.1]hexan-4-ylmethoxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	436.3
51		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(fluoromethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	372.2
53		1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclopropane-1-carbonitrile	419.3
54		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	444.3
55		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(3-fluorooxetan-3-yl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	428.3

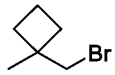
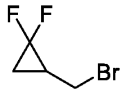
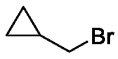
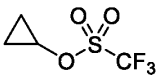
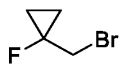
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
56		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	426.3
57		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	410.2
58		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	409.2
59		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	410.2
60		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	444.3
61		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopentyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	458.2

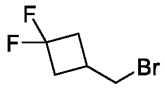
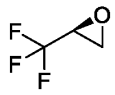
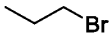
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
62		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-dimethylpropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	410.3
63		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	414.3
64		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	462.3
65		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	424.3
66		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	462.3
67		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	422.3

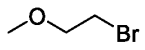
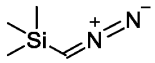
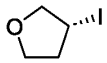
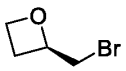
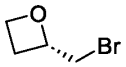
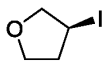
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
69		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-ethoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	368.2
71		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(cyclopropylmethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	394.2
72		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopropyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	430.1
73		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(cyclobutylmethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	408.3
75		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	414.2
76		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	468.2

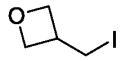
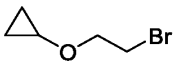
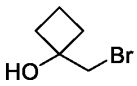
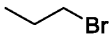
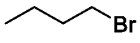
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
77		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	480.2
78		1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile	449.3
79		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(3,3-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	474.2
80		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	460.2
81		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-($^{2}H_{5}$)ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	389.2

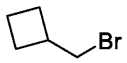
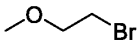
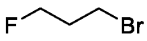
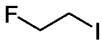
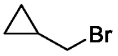
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
82		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[cyclopropyl($^2H_2$)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	412.2
83		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	430.3
84		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2,2-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	474.1
85		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	478.4
86		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(3,3-difluorocyclobutoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	446.2
87		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	478.2

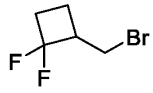
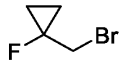
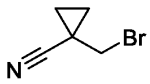
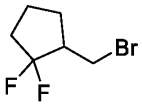
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
88		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	438.3
90		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-cyclobutoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	410.1
91		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2,2-difluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	446.1
92		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(cyclopropylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	410.3
93		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-cyclopropoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	396.1
94		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	428.2

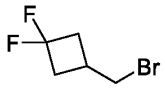
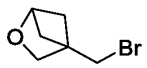
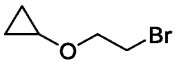
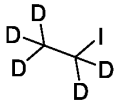
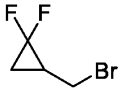
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
95		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(3,3-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	460.3
98		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	468.1
99		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	414.3
100		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	412.3
101		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	398.2
102		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	398.2

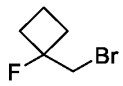
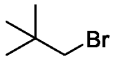
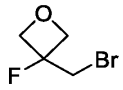
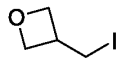
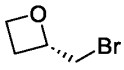
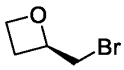
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
103		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	414.3
104		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	412.1
105		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	370.1
106		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(3*S*)-oxolan-3-yloxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	426.1
107		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	426.1
108		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	426.1
109		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(3*R*)-oxolan-3-yloxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	426.3

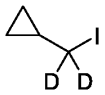
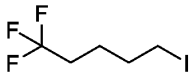
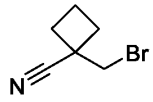
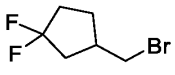
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
110		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	426.1
111		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(2-cyclopropoxyethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	440.1
112		(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	440.3
113		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	444.0
114		(2*R*,3*R*,11b*R*)-8-bromo-9-butoxy-3-(*tert*-butoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	458.1
115		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	444.2

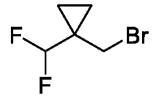
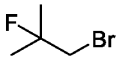
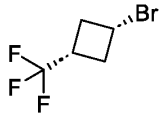
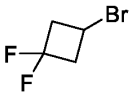
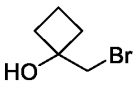
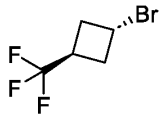
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
116		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(cyclobutylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	470.2
117		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	458.2
118		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	460.1
119		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	428.1
120		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(3-fluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	462.2
121		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-fluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	446.2
122		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(cyclopropylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	456.2

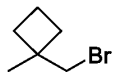
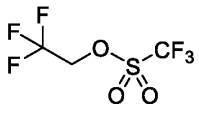
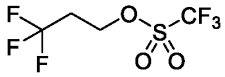
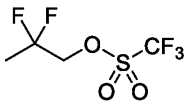
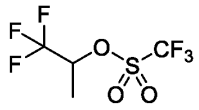
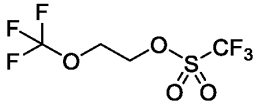
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
123		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	506.2
124		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	474.2
125		1-({[(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclopropane-1-carbonitrile	481.2
126		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-cyclobutoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	456.1
127		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	520.2

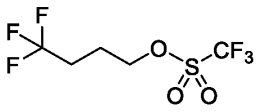
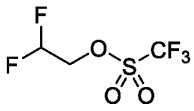
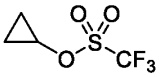
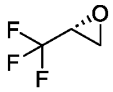
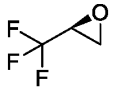
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
128		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	506.1
129		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-{2-oxabicyclo[2.1.1]hexan-4-ylmethoxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	498.2
130		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-cyclopropoxyethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	486.2
131		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^{2}H_5$)ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	435.2
132		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(fluoromethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	434.1
133		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	492.1

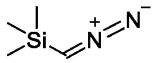
Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
134		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-fluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	488.2
135		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-dimethylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	472.1
136		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3-fluorooxetan-3-yl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	488.2
137		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	472.1
138		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	469.1
139		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	469.1

Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
140		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	458.2
141		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	456.2
142		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	524.2
143		1-({[(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile	495.2
144		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3,3-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	518.2

Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
145		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	506.1
146		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	476.2
147		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	522.2
148		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(3,3-difluorocyclobutoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	492.1
149		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	486.1
150		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	524.2

Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
151		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	484.2
152		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	484.0
153		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	498.1
154		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	480.2
155		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1,1,1-trifluoropropan-2-yl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	496.1
156		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[2-(trifluoromethoxy)ethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	512.1

Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
157		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(4,4,4-trifluorobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	512.2
158		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	466.0
159		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-cyclopropoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	442.1
160		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	514.3
161		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	513.9
162		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	458.2

Cmpd No.	Reagent	Chemical Name	Obs. Ion (m/z)
163		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	460.1
164		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-hydroxy-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	474.2
165		(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol	416.0

[1] Mixture of *trans* isomers (cyclopropyl).

[2] Mixture of *cis* isomers (cyclopropyl).

EXAMPLE 20: Methods for Determining VMAT2 Inhibitory Activity.

Examples of techniques for determining the capability of a compound to inhibit VMAT2 are provided below. The procedure was adapted from that described previously (see, *e.g.*, Near, (1986), Mol. Pharmacol. 30: 252-57; Teng, *et al.*, J. Neurochem. 71, 258-65, 1998). Homogenates from human platelets were prepared by homogenization and then washed by centrifugation as described previously (see, *e.g.*, Hoare *et al.*, (2003) Peptides 24:1881-97). Membrane preparations from HEK293-FL-TRex hVMAT2 cells were prepared as follows:

HEK293-FL-TREx hVMAT2 cells were cultured in growth media consisting of DMEM/F12 + Glutamax, Tet-Negative FBS, 1% Penicillin/Streptomycin, 15 µg/mL Blasticidin and 0.18 mg/mL Hygromycin B. 24 hours prior to harvesting cells, growth media was replaced with induction media consisting of growth media without Blasticidin and Hygromycin B and including 2 µg/mL doxycycline. After harvesting, the resulting cell pellet was re-suspended in ice-cold lysis buffer (50 mM Tris-HCl, 5 mM MgCl2, 1 mM EDTA, pH 7.4, Sigma Aldrich) and the cell suspension was homogenized using a hand-held homogenizer (30,000 rpm at 4°C for 20 seconds) and then left at 4°C for 20 minutes. The cells were further lysed using nitrogen cavitation at 900 psi for 30 minutes at 4°C, and the cell lysate was centrifuged at 3,500 rpm for 10 min at 4°C. The pellet was discarded, and the supernatant was centrifuged at 18,000 rpm at 4°C for 20 min. The resulting pellet was re-suspended in cold lysis buffer and centrifuged again at 18,000 rpm at 4°C for 20 min. The final pellet was re-

suspended in VMAT2 binding buffer (25 mM HEPES, 120 mM NaCl, 5 mM KCl, pH 7.4 with NaOH). Protein was quantified using the Coomassie method (Pierce, Rockford, IL) using bovine serum albumin as the standard.

The human VMAT2 K_i values for the compounds listed in **Table 4** were determined using the following procedures:

Competition binding experiments using HEK293-hVMAT2 membranes: Compound dilution series in DMSO were generated directly from DMSO stock solutions using an Echo 655 (Beckman). In a total volume of 0.150 mL in low-binding 96-well plates (Corning #3605), twelve concentrations of test compound were competed against 10 nM ^{3}H-dihydrotetrabenezine (American Radiolabeled Chemicals) on HEK293-hVMAT2 membranes (7 μg membrane protein per well) in VMAT2 binding buffer (25 mM HEPES, 120 mM NaCl, 5 mM KCl, pH 7.4 with NaOH). Following incubation at 25°C for 90 minutes, bound radioligand was collected by rapid filtration onto GF/C PEI (polyethylenimine) coated filter plates (Perkin Elmer # 6055090) and washed four times with 0.150 mL DPBS (Corning, #21-031-CM) using a Microlab Star (Hamilton). The filter plates were dried overnight and bound radioligand was quantified by scintillation counting using a Microplate Counter Microbeta (PerkinElmer). Data from 12-point concentration response curves were analyzed to calculate an IC_{50} using a four-parameter logistic regression algorithm. The K_i value for each compound was calculated using the Cheng-Prusoff equation, utilizing a K_d of 2.9 nM for ^{3}H-dihydrotetrabenezine.

Competition binding experiments using human platelet homogenates: Compound dilution series in DMSO were generated from either powder stocks by hand or direct dilution using an Echo 655 (Beckman). In a total volume of 0.145mL in low-binding 96-well plates (Corning #3605), twelve concentrations of test compound were competed against 10 nM ^{3}H-dihydrotetrabenezine (American Radiolabeled Chemicals) on human platelet homogenate (30 μg membrane protein per well) in VMAT2 binding buffer (25 mM HEPES, 120 mM NaCl, 5 mM KCl, pH 7.4 with NaOH). Following incubation at 25°C for 90 minutes, bound radioligand was collected by rapid filtration onto GF/C PEI (polyethylenimine) coated filter plates (Perkin Elmer # 6055090) and washed four times with 0.150 mL DPBS (Corning, #21-031-CM) using a Microlab Star (Hamilton). The filter plates were dried overnight and bound radioligand was quantified by scintillation counting using a Microplate Counter Microbeta (PerkinElmer). Data from 12-point concentration response curves were analyzed to calculate an IC_{50} using a four-parameter logistic regression algorithm. The K_i value for each compound was calculated using the Cheng-Prusoff equation, utilizing a K_d of 4.06 nM for ^{3}H-dihydrotetrabenezine.

Table 4

Cmpd No.	VMAT2 K_i (nM) HEK293	VMAT2 K_i (nM) Platelets	Cmpd No.	VMAT2 K_i (nM) HEK293	VMAT2 K_i (nM) Platelets
1	1.2	NT	**84**	3.9	NT
2	2	NT	**85**	6.6	NT
3	73	NT	**87**	1.9	NT
4	443	NT	**88**	6.0	NT
5 [1]	1.20	NT	**89**	NT	0.58
6 [2]	0.86	NT	**90**	NT	1.1
7 [1]	0.67	NT	**91**	NT	0.61
8	0.45	NT	**92**	NT	0.49
9	7.8	NT	**93**	NT	1.5
10	1.5	NT	**94**	0.64	0.91
11	1.2	NT	**95**	0.87	1.1
12	0.93	NT	**96**	NT	0.39
13	6.7	NT	**97**	NT	0.61
14	2.6	NT	**98**	NT	8.4
16	1.0	NT	**99**	NT	10
17	0.90	NT	**100**	0.60	0.77
18	1.7	NT	**101**	NT	0.38
19	0.39	NT	**102**	NT	33
20	384	NT	**103**	NT	8.6
21	0.60	NT	**104**	NT	8.5
22	1.4	NT	**105**	NT	6.7
23	1.0	NT	**106**	NT	11
24	1.4	NT	**107**	NT	7.1
25	31	NT	**108**	NT	17
26	6.4	NT	**109**	NT	24
27	1.0	NT	**110**	NT	6.1
28	1.8	NT	**111**	NT	10
29	14	NT	**112**	2.5	NT
30	6.3	NT	**113**	0.47	NT
31	47	NT	**114**	0.41	NT
32	14	NT	**115**	104	NT
33	52	NT	**116**	0.83	NT

Cmpd No.	VMAT2 K_i (nM) HEK293	VMAT2 K_i (nM) Platelets
34	7.2	NT
35	1.6	NT
36	6.5	NT
37	29	NT
38	1.0	NT
39	2.7	NT
40	0.65	NT
41	0.58	NT
42	6.8	NT
43	16	NT
44	56	NT
45	1.7	NT
46	4.0	NT
47	35	NT
48	0.72	NT
49	1.1	NT
50	50	NT
51	44	NT
52	2.0	NT
53	78	NT
54	0.96	NT
55	4.9	NT
56	0.82	NT
57	193	NT
58	201	NT
59	99	NT
61	4.7	NT
62	4.1	NT
64	1.4	NT
65	12	NT
66	0.65	NT
67	5.2	NT
68	1.1	NT

Cmpd No.	VMAT2 K_i (nM) HEK293	VMAT2 K_i (nM) Platelets
117	9.7	NT
118	8.9	NT
119	2.7	NT
120	1.3	NT
121	2.1	NT
122	0.69	NT
123	2.4	NT
124	1.1	NT
125	35	NT
126	2.8	NT
127	6.9	NT
128	1.1	NT
129	20	NT
130	6.5	NT
131	1	NT
132	55	NT
133	0.62	NT
134	0.98	NT
135	31	NT
136	3.2	NT
137	118	NT
140	0.92	NT
141	0.20	NT
142	19	NT
143	74	NT
144	1.3	NT
145	2.3	NT
147	19	NT
148	2.5	NT
149	4.8	NT
150	14	NT
151	12	NT
152	0.7	NT

Cmpd No.	VMAT2 K_i (nM) HEK293	VMAT2 K_i (nM) Platelets
69	2.0	NT
70	1.5	NT
71	0.68	NT
72	0.55	NT
73	0.58	NT
74	8.1	NT
75	17	NT
76	9.7	NT
77	12	NT
78	59	NT
79	0.25	NT
80	1.3	NT
81	0.95	NT
82	0.24	NT

Cmpd No.	VMAT2 K_i (nM) HEK293	VMAT2 K_i (nM) Platelets
153	0.86	NT
154	1.0	NT
155	446	NT
156	0.87	NT
157	0.58	NT
158	1.9	NT
159	1.7	NT
160	4.0	NT
161	6.5	NT
162	27	NT
163	10	NT
164	7.3	NT
165	5.2	NT
166	6.7	NT

NT = Not Tested

[1] Assayed as a mixture of *trans* isomers (cyclopropyl).

[2] Assayed as a mixture of *cis* isomers (cyclopropyl).

EXAMPLE 21: VMAT2 Inhibitor-Induced Reduction of Open-Field Hypolocomotor Activity.

The effect of VMAT2 inhibitors on dopamine depletion is measured using the locomotor activity (LMA) assay. Following a pre-treatment time of 60 or 120 minutes, male Sprague-Dawley rats (250-350 g) are placed in a locomotor activity chamber surrounded by Infrared PhotoBeams (Med Associates). Rat locomotor activity is detected by automated counting of successive beam breaks and activity is defined as the number of beam breaks in 60 min. Data is analyzed by one-way analysis of variance (ANOVA; GraphPad Prism) followed by Dunnett's post-hoc test for significance. The ED_{50} is calculated for the compound.

EXAMPLE 22: Conditioned Avoidance Response Assay of Antipsychotic Activity.

The conditioned avoidance response (CAR) test has been shown to be an effective and reliable preclinical model for assessing the antipsychotic activity of compounds. In the CAR paradigm, a rat is trained in a two-chamber shuttle box to respond to a conditioned stimulus (auditory) by negative reinforcement. If the animal fails to move to the other chamber upon presentation of an auditory stimulus, a mild foot shock is applied to the side where the rat is located. The rat learns to avoid the mild foot shock by moving to the other chamber upon initiation of the auditory signal,

termed a conditioned avoidance response. Crossing to the other chamber during administration of the shock is termed an escape response. If a rat fails to move to the other chamber even upon administration of the foot shock, the rat is considered to have an escape failure. Numerous studies have shown that typical and atypical antipsychotic drugs selectively suppress CAR, thus making it an ideal assay to screen potential antipsychotic compounds (see, *e.g.*, Wadenberg *et al.*, Biobehav. Rev. (1999) 23: 851-62).

Male Wistar rats are trained every day for 3 to 4 weeks. In the training session, rats are placed in the CAR two-way shuttle box and the training period of 20 trials ensued. A trial consisted of a 10-sec presentation of an 80 dB white noise followed by a scrambled 0.65 mA foot shock lasting up to 20 sec. The inter-trial interval ranged from 20-60 sec. The rat learns to avoid shock by moving from one compartment to the other when the conditioned stimulus is presented (a conditioned avoidance response). A rat is deemed sufficiently trained if it avoided the shock when presented with the conditioned stimulus at least 16 times out of the 20 trials. Rats that do not pass these criteria are not used.

On test day, trained animals are acclimated in the test room for 30 minutes prior to testing. They are then dosed with compound and are placed in the CAR two-way shuttle box. In the test, 20 trials are performed on each rat. In each trial the conditioned stimulus is applied (10-sec presentation of 80 dB white noise), followed by the foot shock (a scrambled 0.65 mA foot shock lasting up to 20 sec). If the animal moves to the other chamber on presentation of the conditioned stimulus, it is scored as a conditioned avoidance response. If it moved upon presentation of the foot shock, it is scored as an escape. If it fails to move upon presentation of the foot shock, it is scored as an escape failure. Antipsychotic efficacy is evident by an increase in the number of escapes. Data are analyzed by analysis of variance (ANOVA) or Kruskal-Wallis followed by post-hoc comparisons with Dunnett's or Dunn's when appropriate. An effect is considered significant if $p < 0.05$.

EXAMPLE 23: Method to Determine Stability of Compounds in Human Liver Microsomes.

A test compound (0.5 μM) was incubated with pooled mixed gender liver microsomes from humans (0.5mg/mL total protein) at 37°C in the presence of an NADPH-generating system containing 50 mM, pH 7.4 potassium phosphate buffer, 3 mM magnesium chloride, 1 mM EDTA, 1 mM NADP, 5 mM glusose-6-phosphate, and 1 Unit/mL glucose-6-phosphate dehydrogenase. All concentrations were relative to the final incubation volume of 125 μL. Incubations were conducted at 37°C for 0, 5, 10, 20, 40, and 60 minutes in a water bath and terminated by rapid mixing with 150 μL of ice-cold acetonitrile containing internal standard. Precipitated proteins were removed by centrifugation prior to LC-MS/MS analysis. Aliquots of the resulting supernatant fractions were analyzed by LC-MS/MS monitoring for depletion of parent compound. The resultant peak area ratio versus time data was fitted to a non-linear regression using XLfit Scientific Curve Fitting Software (IDBS Ltd., Surrey, UK) and the elimination half-life ($t_{1/2}$, min) was calculated from the slope. Pharmacokinetic parameters were

predicted using the method described by Obach *et al.* (J. Pharmcol. Exp. Ther. 1997; 283: 46.58). Briefly, the values for intrinsic clearance were calculated from the elimination half-life data and were then scaled to represent the clearance expected in the entire animal, see **Table 5** (human). Additional values calculated included predicted extraction ratio and predicted maximum bioavailability.

For very stable compounds the *in vitro* half-life calculated from the HLM method is maxed at 420 minutes. Accordingly, for these stable compounds the *in vitro* half-life is at least 420 minutes but could be greater. Further, for these stable compounds the predicted systemic clearance and scaled intrinsic clearance is at least 2.59 and 2.97 respectively but could be lower, and the predicted maximum bioavailability (%F) is at least 87 but could be higher.

Table 5 (Human LM)

Cmpd. No.	HLM Elimination half-life ($t_{1/2}$, min)	HLM Predicted Systemic Clearance (mL/min/kg)	HLM Scaled Intrinsic Clearance (mL/min/kg)	Predicted Max. Bioavailability (%F)
1	≥ 420	2.59	2.97	87.07
2	373.5	2.86	3.34	85.70
5 [1]	27.5	13.88	45.41	30.58
6 [2]	≥ 420	2.59	2.97	87.07
7 [1]	≥ 420	2.59	2.97	87.07
8	38.5	12.37	32.41	38.16
9	181.3	5.12	6.88	74.40
10	11.7	16.84	106.75	15.78
11	22.8	14.65	54.71	26.77
12	2.1	19.35	595.90	3.25
13	262.1	3.84	4.76	80.78
16	288.1	3.56	4.33	82.22
17	182.4	5.10	6.84	74.51
18	≥ 420	2.59	2.97	87.07
21	≥ 420	2.59	2.97	87.07
22	≥ 420	2.59	2.97	87.07
23	≥ 420	2.59	2.97	87.07
24	≥ 420	2.59	2.97	87.07
27	≥ 420	2.59	2.97	87.07
28	≥ 420	2.59	2.97	87.07
30	≥ 420	2.59	2.97	87.07
34	≥ 420	2.59	2.97	87.07

Cmpd. No.	HLM Elimination half-life ($t_{1/2}$, min)	HLM Predicted Systemic Clearance (mL/min/kg)	HLM Scaled Intrinsic Clearance (mL/min/kg)	Predicted Max. Bioavailability (%F)
35	20	15.14	62.38	24.28
37	86	8.43	14.57	57.86
38	79	8.80	15.70	56.02
39	≥ 420	2.59	2.97	87.07
40	103	7.53	12.08	62.35
41	33	13.06	37.67	34.68
42	≥ 420	2.59	2.97	87.07
45	202	4.72	6.18	76.40
46	≥ 420	2.59	2.97	87.07
48	72.4	9.25	17.22	53.74
49	≥ 420	2.59	2.97	87.07
52	≥ 420	2.59	2.97	87.07
54	≥ 420	2.59	2.97	87.07
55	335.3	3.14	3.72	84.33
56	21.4	14.88	58.20	25.58
61	35.1	12.80	35.56	36.00
64	≥ 420	2.59	2.97	87.07
65	195.2	4.84	6.39	75.79
66	≥ 420	2.59	2.97	87.07
67	15.4	16.04	81.09	19.78
68	≥ 420	2.59	2.97	87.07
69	≥ 420	2.59	2.97	87.07
70	≥ 420	2.59	2.97	87.07
71	≥ 420	2.59	2.97	87.07
72	≥ 420	2.59	2.97	87.07
73	13	16.62	98.16	16.93
74	≥ 420	2.59	2.97	87.07
75	≥ 420	2.59	2.97	87.07
79	76	8.99	16.34	55.04
80	≥ 420	2.59	2.97	87.07
81	≥ 420	2.59	2.97	87.07
82	227	4.32	5.50	78.43

Cmpd. No.	HLM Elimination half-life ($t_{1/2}$, min)	HLM Predicted Systemic Clearance (mL/min/kg)	HLM Scaled Intrinsic Clearance (mL/min/kg)	Predicted Max. Bioavailability (%F)
89	≥ 420	2.59	2.97	87.07
90	65	9.76	19.07	51.19
91	120	6.84	10.41	65.78
92	140	15.56	20.01	77.77
93	232	4.24	5.37	78.82
94	235	4.19	5.30	79.07
95	143	6.07	8.71	69.65
96	≥ 420	2.59	2.97	87.07
97	≥ 420	2.59	2.97	87.07
98	≥ 420	2.59	2.97	87.07
99	≥ 420	2.59	2.97	87.07
100	48	11.34	26.20	43.29
101	122	6.77	10.24	66.14
103	≥ 420	2.59	2.97	87.07
104	192	4.90	6.49	75.51
105	261	3.86	4.78	80.71
106	152	5.81	8.2	70.93
107	147	5.96	8.48	70.22
108	164	5.51	7.61	72.45
109	115	7.02	10.82	64.89
110	203	4.70	6.15	76.49
111	22	14.86	57.84	25.69
113	163	5.54	7.67	72.29
114	34	12.71	36.43	36.43
116	52	15.20	24.02	24.02
119	≥ 420	2.59	2.97	87.07
120	≥ 420	2.59	2.97	87.07
121	≥ 420	2.59	2.97	87.07
122	93	8.03	13.42	59.85
123	142	6.11	8.80	69.45
124	298	3.46	4.19	82.71
128	161	5.59	7.76	72.04

Cmpd. No.	HLM Elimination half-life ($t_{1/2}$, min)	HLM Predicted Systemic Clearance (mL/min/kg)	HLM Scaled Intrinsic Clearance (mL/min/kg)	Predicted Max. Bioavailability (%F)
131	≥ 420	2.59	2.97	87.07
133	133	6.37	9.35	68.14
134	58	10.36	21.50	48.19
136	269	3.76	4.63	81.21
140	224	4.35	5.56	78.24
141	59	10.32	21.32	48.41
144	108	7.34	11.59	63.30
145	≥ 420	2.59	2.97	87.07
148	150	5.88	8.32	70.63
152	≥ 420	2.59	2.97	87.07
153	≥ 420	2.59	2.97	87.07
156	179.0	5.17	6.97	74.14
157	≥ 420	2.59	2.97	87.07
159	≥ 420	2.59	2.97	87.07
165	296.3	3.48	4.21	82.60
166	≥ 420	2.59	2.97	87.07

[1] Assayed as a mixture of *trans* isomers (cyclopropyl).

[2] Assayed as a mixture of *cis* isomers (cyclopropyl).

NA = Not Available

EXAMPLE 24: Method to determine cytochrome P450 2D6 3A4 (CYP3A4) and (CYP2D6) inhibition in expressed human enzymes using fluorescent marker substrates.

A test compound was incubated with individually expressed human recombinant CYP enzymes systems in the presence of NADPH and IC_{50} values for inhibition were determined using a marker substrate approach.

For CYP3A4, the test compound was incubated with expressed human CYP3A4 (Gentest Supersomes (Corning, Woburn, MA)) and IC_{50} values for inhibition were determined using marker substrate 7-benzyloxy-4-(trifluoromethyl)-coumarin (BFC), which is dealkylated by CYP3A4 to form the fluorescent product, 7-hydroxy-4-(trifluoromethyl)-coumarin (7-HFC). The amount of 7-HFC formed during the incubation was detected with a 96-well fluorescent plate reader (BioTek Synergy LX, Agilent, Santa Clara, CA), excitation λ 400 nm and emission λ 528 nm.

For CYP2D6, the test compound was incubated with expressed human CYP2D6 (Gentest Supersomes, (Corning, Woburn, MA)) and IC_{50} values for inhibition were determined using marker

substrate, 3-[2-(*N*,*N*-diethyl-*N*-methylamino) ethyl]-7-methoxy-4-methylcoumarin (AMMC), which is O-demethylated by CYP2D6 to form the fluorescent product, 3-[2-(*N*,*N*-diethyl-*N*-methylammonium)ethyl]-7-hydroxy-4-methylcoumarin (AHMC). The amount of AHMC formed during the incubation was monitored with a 96-well fluorescent plate reader (BioTek Synergy LX, Agilent, Santa Clara, CA), excitation λ 360 nm and emission λ 460 nm.

For each enzyme assay, four concentrations of the test compound (ranging from 0.048 to 6 μM) were assessed at a single concentration of the substrate (K_m), 50 μM for BFC and 1.5 μM for AMMC, respectively, in duplicate. Reactions (total volume 200μL) included 100 μL of NADPH-generating system containing 75 mM, pH 7.4 potassium phosphate buffer, 3 mM magnesium chloride, 1 mM NADP, 5 mM glusose-6-phosphate, and 1 unit/mL glucose-6-phosphate and were initiated with 100 μL of CYP enzyme solution (10 pmol), which was added immediately before the samples were incubated at 37°C. Incubations are stopped after 30 minutes by adding 75μL stop solution (80% acetonitrile / 20% 0.5M Tris Base). Ketoconazole and quinidine were used for positive controls of CYP3A4 and CYP2D6, respectively.

For each CYP, the extent of inhibition, expressed as a percentage, was calculated then data were plotted on a semi-log plot [log (inhibitor) on the x-axis and percentage of control activity on the y-axis], and fitted with the following Levenberg-Marquardt algorithm:

$$y = A + \frac{(B - A)}{1 + (C / X)^D}$$

Where "*A*" is the bottom plateau of the curve and usually is equal to 0, "*B*" is the top plateau of the curve and has a typical value of 100, "*C*" represents "*X*" value at the middle of the curve, which represents the concentration of the inhibitor that causes 50% inhibition, "*D*" is the slope factor. The IC_{50} value was calculated using XLfit Scientific Curve Fitting Software (IDBS Ltd., Surrey, UK). The IC_{50} values for certain compounds against CYP2D6 and CYP3A4 are provided in **Table 6**.

Table 6

Cmpd No.	CYP2D6 IC_{50} (nM)	CYP3A4 IC_{50} (nM)	Cmpd No.	CYP2D6 IC_{50} (nM)	CYP3A4 IC_{50} (nM)
1	> 6,000	> 6,000	71	> 6,000	> 6,000
2	> 6,000	> 6,000	72	> 6,000	> 6,000
6 [2]	> 6,000	> 6,000	74	> 6,000	> 6,000
7 [1]	> 6,000	> 6,000	75	> 6,000	> 6,000
13	> 6,000	> 6,000	80	> 6,000	> 6,000
16	> 6,000	> 6,000	81	> 6,000	> 6,000
18	> 6,000	> 6,000	82	> 6,000	> 6,000
21	> 6,000	> 6,000	89	> 6,000	> 6,000
22	> 6,000	> 6,000	92	> 6,000	> 6,000

Cmpd No.	CYP2D6 IC_{50} (nM)	CYP3A4 IC_{50} (nM)	Cmpd No.	CYP2D6 IC_{50} (nM)	CYP3A4 IC_{50} (nM)
23	> 6,000	> 6,000	93	> 6,000	> 6,000
24	> 6,000	> 6,000	96	> 6,000	> 6,000
27	> 6,000	> 6,000	97	> 6,000	> 6,000
28	> 6,000	> 6,000	103	> 6,000	> 6,000
30	> 6,000	> 6,000	104	> 6,000	> 6,000
34	> 6,000	> 6,000	105	> 6,000	> 6,000
39	> 6,000	> 6,000	110	> 6,000	> 6,000
42	> 6,000	> 6,000	119	> 6,000	> 6,000
45	> 6,000	> 6,000	120	> 6,000	> 6,000
46	> 6,000	> 6,000	124	> 6,000	> 6,000
49	> 6,000	> 6,000	131	> 6,000	> 6,000
52	> 6,000	> 6,000	136	> 6,000	> 6,000
54	> 6,000	> 6,000	140	> 6,000	> 6,000
55	> 6,000	> 6,000	145	> 6,000	> 6,000
64	> 6,000	> 6,000	152	> 6,000	> 6,000
65	> 6,000	> 6,000	153	> 6,000	> 6,000
66	> 6,000	> 6,000	157	> 6,000	> 6,000
68	> 6,000	> 6,000	159	> 6,000	> 6,000
69	> 6,000	> 6,000	165	> 6,000	> 6,000
70	> 6,000	> 6,000	166	> 6,000	> 6,000

[1] Assayed as a mixture of *trans* isomers (cyclopropyl).

[2] Assayed as a mixture of *cis* isomers (cyclopropyl).

EXAMPLE 25: Protocol for testing activity of compounds against hERG.

The objective of these studies was to examine the *in vitro* effects of compounds on the hERG (human ether-a-go-go-related gene) channel current (a surrogate for I_{Kr}, the rapidly activating delayed rectifier cardiac potassium current; see, *e.g.*, Redfern *et al.*, Cardiovascular Research (2003) 58(1):32-45). The concentration-response relationship for certain compounds on the hERG potassium channel current was evaluated at room temperature in stably transfected mammalian cells that express cloned hERG potassium channels, encoded by the *KCNH2* gene. The hERG potassium channels were expressed in Chinese Hamster's Ovary (CHO) cells that lack endogenous I_{Kr}.

The cardiac potassium channel hERG is responsible for a rapid delayed rectifier current (I_{Kr}) in human ventricles. Inhibition of I_{Kr} is the most common cause of cardiac action potential prolongation by non-cardiac drugs (see, *e.g.*, Brown and Rampe, Pharmaceutical News (2000) 7:15-

20; Weirich and Antoni, Basic Res. Cardiol. (1998) 93 Suppl 1:125-132; Yap and Camm, Clin Exp. Allergy (1999) 29 Suppl 3:174-181). Increased action potential duration causes prolongation of the QT interval and is associated with *torsade de pointes* (see, *e.g.*, Brown and Rampe, Pharmaceutical News (2000) 7:15-20).

hERG positive control: Stock solutions of the positive control article were prepared in DMSO and stored at room temperature.

Control #1	
Name:	Dofetilide
Source:	Sigma (Cat# PZ0016)
Molecular Weight:	441.56
Storage Conditions:	Room Temperature

Control #2	
Name:	Verapamil HCl
Source:	Tocris (Cat#0654)
Molecular Weight:	491.07
Storage Conditions:	Room Temperature

CHO/hERG Cell Line:

CHO/hERG Cell Line	
Organism:	*Cricetulus griseus*
Designation:	Chinese Hamster's Ovary (CHO)
Tissue:	Ovary; transfected with ion channel cDNA
Morphology:	Epithelial
Age/Stage:	Embryo
Source Strain:	ATCC, Manassas, VA
Source Substrain:	Charles River Laboratories

CHO Culture: CHO cells were stably transfected with hERG cDNA. Stable transfectants were maintained in the culture medium with the appropriate selection pressure and antibiotics.

Test Method:

1. Cell Treatments: All experiments were performed at room temperature. Each cell was treated as its own control. Full block was achieved with the addition of 20μM Verapamil.

Test Article Treatment Groups, 6-point dose response curve is generated. 1:4 serial dilutions were made from the top concentration of 12μM.

2. Automated Patch Clamp Procedure

a. Platform: For all hERG testing, the 384-well based automated Patch Clamp System SyncroPatch 384PE from Nanion Technologies with PatchControl software (data acquisition) and DataControl software (data analysis) was used. The recordings were performed at room temperature (22°C) on planar NPC-384 multi-hole chips with 4 holes per well at a medium resistance.

b. The recordings were executed in whole cell patch mode. The composition of the internal solution was: 10 mM EGTA, 10 mM HEPES, 10 mM KCl, 10 mM NaCl and 110 mM KF, pH 7.2,
mOsm = 285. The composition of the external solution was: 10 mM HEPES, 80 mM NaCl, 60 mM NMDG, 5 mM Glucose, 4 mM KCl, 5 mM $CaCl_2$ and 1 mM $MgCl_2$, pH 7.4, mOsm = 298.

c. Compound preparation: All compounds were solvated in 100% DMSO. On the day of the experiment, a serial dilution in DMSO was prepared using the Echo 655 acoustic liquid handler. The pre-diluted compounds were further diluted into external solution with a dilution factor of 1:500 (0.2% DMSO by volume).

d. Compound acquisition mode: Single application of compounds was used with concentrations across the chip. Every well received once compound concentration followed by a full block of Verapamil to assess the leak current. Different concentrations of each compound to generate individual dose response relationships were spread across the chip.

e. Onset and block of hERG current was measured using a stimulus voltage pattern consisting of a 500ms prepulse to -40mV (leakage subtraction), a 2-second activating pulse to +40mV followed by a 2-second test pulse to -40mV followed by a 2-second test pulse to -40mV. The pulse pattern was repeated continuously at 6 s intervals from a holding potential of -80 mV. Peak tail current was calculated from the current amplitude evoked by the -40 mV prepulse and subtracted from the total membrane current record. A small hyperpolarizing voltage step from -80 to -90 mV was implemented during holding potential to calculate the resistance according to Ohm's law for quality control.

3. Data Analysis

Data was stored on the Neurocrine Biosciences computer network for off-line analysis. Data acquisition and analysis was performed using Nanion Data Control software. Steady state is defined by the limiting constant rate of change with time (linear time dependence). The steady state before and after test article application was used to calculate percentage of current inhibited at each concentration.

The IC_{50} values for certain compounds against hERG are provided in **Table 7**.

Table 7

Cmpd No.	hERG IC_{50} (nM)	Cmpd No.	hERG IC_{50} (nM)
1	> 12,000	**82**	> 12,000
2	> 12,000	**84**	7,598
3	> 12,000	**85**	5,091
5 [1]	> 12,000	**87**	10,292
6 [2]	> 12,000	**88**	7,508

Cmpd No.	hERG IC_{50} (nM)
7 [1]	> 12,000
8	> 12,000
9	> 12,000
10	> 12,000
11	> 12,000
12	> 12,000
13	> 12,000
14	7,344
16	> 12,000
17	> 12,000
18	> 12,000
19	8,967
21	> 12,000
22	> 12,000
23	> 12,000
24	> 12,000
25	> 12,000
26	> 12,000
27	> 12,000
28	> 12,000
29	> 12,000
30	> 12,000
31	> 12,000
32	> 12,000
33	> 12,000
34	> 12,000
35	> 12,000
36	7,387
37	> 12,000
38	> 12,000
39	> 12,000
40	> 12,000
41	> 12,000

Cmpd No.	hERG IC_{50} (nM)
89	> 12,000
90	> 12,000
91	> 12,000
92	> 12,000
93	> 12,000
94	> 12,000
95	> 12,000
96	> 12,000
97	> 12,000
98	> 12,000
99	> 12,000
100	> 12,000
101	> 12,000
102	> 12,000
103	> 12,000
104	> 12,000
105	> 12,000
106	> 12,000
107	> 12,000
108	> 12,000
109	> 12,000
110	> 12,000
111	> 12,000
112	> 12,000
113	> 12,000
114	> 12,000
116	10,982
117	> 12,000
118	9,096
119	> 12,000
120	> 12,000
121	> 12,000
122	> 12,000

Cmpd No.	hERG IC_{50} (nM)
42	> 12,000
43	> 12,000
44	> 12,000
45	> 12,000
46	> 12,000
47	> 12,000
48	> 12,000
49	> 12,000
50	> 12,000
51	> 12,000
52	> 12,000
53	> 12,000
54	> 12,000
55	> 12,000
56	> 12,000
57	> 12,000
58	> 12,000
59	> 12,000
61	> 12,000
62	> 12,000
64	> 12,000
65	> 12,000
66	> 12,000
67	6,107
68	> 12,000
69	> 12,000
70	> 12,000
71	> 12,000
72	> 12,000
73	> 12,000
74	> 12,000
75	> 12,000
76	> 12,000

Cmpd No.	hERG IC_{50} (nM)
123	> 12,000
124	> 12,000
126	> 12,000
127	6,832
128	7,503
129	> 12,000
130	> 12,000
131	> 12,000
133	> 12,000
134	> 12,000
136	> 12,000
137	4,532
140	> 12,000
141	> 12,000
142	3,390
143	> 12,000
144	4,918
145	10,656
147	5,399
148	9,222
149	> 12,000
150	8,912
151	5,557
152	> 12,000
153	> 12,000
154	> 12,000
156	> 12,000
157	> 12,000
158	> 12,000
159	> 12,000
160	> 12,000
161	> 12,000
162	> 12,000

Cmpd No.	hERG IC_{50} (nM)
77	5,706
78	> 12,000
79	5,893
80	> 12,000
81	> 12,000

Cmpd No.	hERG IC_{50} (nM)
163	> 12,000
164	> 12,000
165	> 12,000
166	> 12,000

[1] Assayed as a mixture of *trans* isomers (cyclopropyl).

[2] Assayed as a mixture of *cis* isomers (cyclopropyl).

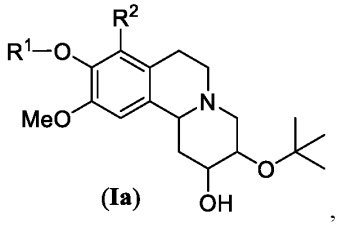
The various embodiments described above can be combined to provide further embodiments. All U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications, and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference in their entirety. Aspects of the embodiments can be modified, if necessary, to employ concepts of the various patents, applications, and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

What is claimed is:

1. A compound of Formula (**Ia**):



(**Ia**),

or a pharmaceutically acceptable salt thereof,

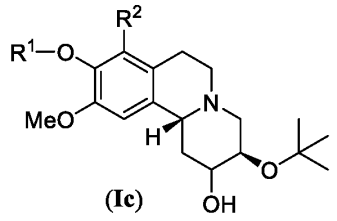
wherein:

R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl; and

R^2 is halogen.

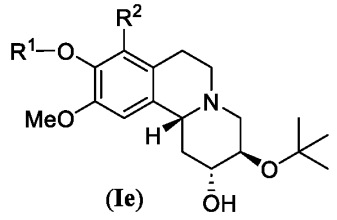
2. The compound of claim 1, wherein the compound is of Formula (**Ic**):



(**Ic**)

or a pharmaceutically acceptable salt thereof.

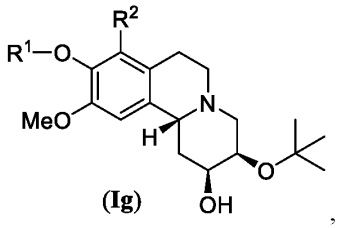
3. The compound of claim 1, wherein the compound is of Formula (**Ie**):



(**Ie**)

or a pharmaceutically acceptable salt thereof.

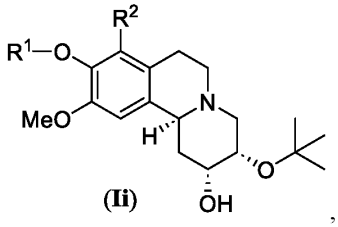
4. The compound of claim 1, wherein the compound is of Formula (**Ig**):



(Ig),

or a pharmaceutically acceptable salt thereof.

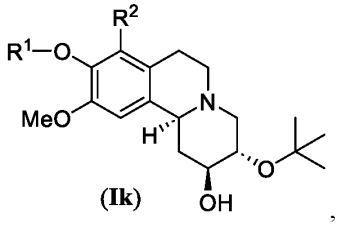
5. The compound of claim 1, wherein the compound is of Formula **(Ii)**:



(Ii),

or a pharmaceutically acceptable salt thereof.

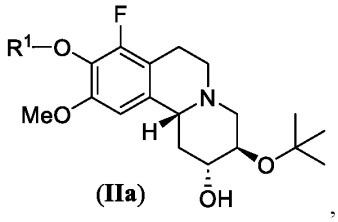
6. The compound of claim 1, wherein the compound is of Formula **(Ik)**:



(Ik),

or a pharmaceutically acceptable salt thereof.

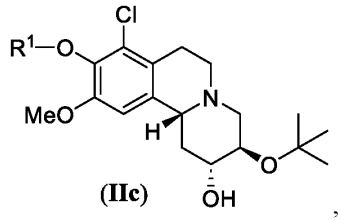
7. The compound of claim 1, wherein the compound is of Formula **(IIa)**:



(IIa),

or a pharmaceutically acceptable salt thereof.

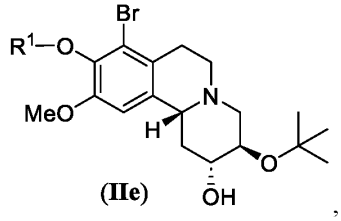
8. The compound of claim 1, wherein the compound is of Formula **(IIc)**:



(IIc),

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, wherein the compound is of Formula **(IIe)**:



(IIe),

or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

11. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C4-alkylene, 4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

12. The compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C4-alkylene,

4-8-membered-heterobicyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

13. The compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, and C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

14. The compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, and C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

15. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, CH_3-O-C_2-alkylene, C_1-C_5-alkyl, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

16. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

17. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-

membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

18. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

19. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, CH_3-O-C_2-alkylene, C_1-C_5-alkyl, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

20. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

21. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

22. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, C_1-C_5-

alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

23. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, CH_3-O-C_2-alkylene, C_1-C_5-alkyl, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

24. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

25. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

26. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

27. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, CH_3-O-C_2-alkylene, C_1-C_5-alkyl, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

28. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, C_3-C_5-cycloalkyl-C_1-C_2-alkylene, cyclopropyl-O-C_2-alkylene, (C_5-C_6-bicycloalkyl)CH_2-, and C_7-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

29. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, (6-membered-heterobicyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

30. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 4-5-membered-heterocyclyl, (4-membered-heterocyclyl)CH_2-, C_1-C_5-alkyl, CH_3-O-C_2-alkylene, C_3-C_4-cycloalkyl, (C_3-C_5-cycloalkyl)CH_2-, and cyclopropyl-O-C_2-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

31. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl,

(cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, oxolanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

32. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

33. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

34. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methylpropyl, oxetanyl, oxolanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

35. The compound according claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl,

ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, oxolanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

36. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

37. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

38. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methylpropyl, oxetanyl, oxolanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

39. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, oxolanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

40. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclobutylethyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

41. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxabicyclo[2.1.1]hexanyl)methyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

42. The compound according to claim 31, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methylpropyl, oxetanyl, oxolanyl, pentyl, and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

43. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1-cyclobutylethyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-

cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, oxolan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

44. The compound according to claim 43, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1-cyclobutylethyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-*d5*, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

45. The compound according to claim 43, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

46. The compound according to claim 43, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, oxolan-3-yl, pentyl, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

47. The compound according to claim 43, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1-

cyclobutylethyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, oxolan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

48. The compound according to claim 43, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1-cyclobutylethyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-*d5*, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

49. The compound according to claim 43, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

50. The compound according to claim 43, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, oxolan-3-yl, pentyl, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methyl, and trifluoromethyl.

51. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 1-cyclobutylethyl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, oxolan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

52. The compound according to claim 51, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 1-cyclobutylethyl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl,

cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

53. The compound according to claim 51, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, and propyl.

54. The compound according to claim 51, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2,2-trifluoroethyl, 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 5,5,5-trifluoropentyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, oxolan-3-yl, propan-2-yl, and propyl.

55. The compound according to claim 51, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-

yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 1-cyclobutylethyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, oxolan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

56. The compound according to claim 51, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 1-cyclobutylethyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

57. The compound according to claim 51, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-

oxabicyclo[2.1.1]hexan-4-yl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, and propyl.

58. The compound according to claim 51, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2,2-trifluoroethyl, 2-cyclopropoxyethyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 5,5,5-trifluoropentyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, oxolan-3-yl, propan-2-yl, and propyl.

59. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*S*)-1-cyclobutylethyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (3*R*)-oxolan-3-yl, (3*S*)-oxolan-3-yl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-

yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 1,1,1-trifluoropropan-2-yl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

60. The compound according to claim 59, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*S*)-1-cyclobutylethyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3s)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 1,1,1-trifluoropropan-2-yl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

61. The compound according to claim 59, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-

hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, and propyl.

62. The compound according to claim 59, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3*R*)-oxolan-3-yl, (3*S*)-oxolan-3-yl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, 2,2,2-trifluoroethyl, 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 5,5,5-trifluoropentyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, propan-2-yl, and propyl.

63. The compound according to claim 59, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*S*)-1-cyclobutylethyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-

yl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (3*R*)-oxolan-3-yl, (3*S*)-oxolan-3-yl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

64. The compound according to claim 59, or a pharmaceutically acceptable salt thereof, wherein: R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*S*)-1-cyclobutylethyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3s)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 1,1,1-trifluoropropan-2-yl, 1-methylcyclobutyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

65. The compound according to claim 59, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-oxabicyclo[2.1.1]hexan-4-yl)methyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, 1,1,1-trifluoropropan-2-yl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, and propyl.

66. The compound according to claim 59, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3*R*)-oxolan-3-yl, (3*S*)-oxolan-3-yl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, 2,2,2-trifluoroethyl, 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 5,5,5-trifluoropentyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, oxetan-3-yl, propan-2-yl, and propyl.

67. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is 3-7-membered-heterocyclyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

68. The compound according to claim 67, or a pharmaceutically acceptable salt thereof, wherein R^1 is 4-5-membered-heterocyclyl.

69. The compound according to claim 67, or a pharmaceutically acceptable salt thereof, wherein: R^1 is selected from: oxetanyl and oxolanyl.

70. The compound according to claim 67, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: oxetan-3-yl and oxolan-3-yl.

71. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is 3-7-membered-heterocyclyl-C_1-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

72. The compound according to claim 71, or a pharmaceutically acceptable salt thereof, wherein: R^1 is (4-membered-heterocyclyl)CH_2 optionally substituted with one substituent selected from: halogen.

73. The compound according to claim 71, or a pharmaceutically acceptable salt thereof, wherein: R^1 is (oxetanyl)methyl optionally substituted with one substituent selected from: fluoro.

74. The compound according to claim 71, or a pharmaceutically acceptable salt thereof, wherein: R^1 is selected from: (oxetan-2-yl)methyl and (oxetan-3-yl)methyl, each optionally substituted with one substituent selected from: fluoro.

75. The compound according to claim 71, or a pharmaceutically acceptable salt thereof, wherein: R^1 is selected from: (3-fluorooxetan-3-yl)methyl, (oxetan-2-yl)methyl, and (oxetan-3-yl)methyl.

76. The compound according to claim 71, or a pharmaceutically acceptable salt thereof, wherein: R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, ((2*S*)-oxetan-2-yl)methyl, (3-fluorooxetan-3-yl)methyl, and (oxetan-3-yl)methyl.

77. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is 4-8-membered-heterobicyclyl-C_1-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

78. The compound according to claim 77, or a pharmaceutically acceptable salt thereof, wherein R^1 is (6-membered-heterobicyclyl)CH_2.

79. The compound according to claim 77, or a pharmaceutically acceptable salt thereof, wherein R^1 is (oxabicyclo[2.1.1]hexanyl)methyl.

80. The compound according to claim 77, or a pharmaceutically acceptable salt thereof, wherein R^1 is (2-oxabicyclo[2.1.1]hexan-4-yl)methyl.

81. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_1-C_4-alkyl-O-C_2-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

82. The compound according to claim 81, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3-O-C_2-alkylene optionally substituted with one, two, or three substituents selected from: halogen.

83. The compound according to claim 81, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3-O-C_2-alkylene optionally substituted with one, two, or three substituents selected from: fluoro.

84. The compound according to claim 81, or a pharmaceutically acceptable salt thereof, wherein R^1 is (methoxy)ethyl optionally substituted with one, two, or three substituents selected from: fluoro.

85. The compound according to claim 81, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 2-(trifluoromethoxy)ethyl and 2-methoxyethyl.

86. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_1-C_6-alkyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

87. The compound according to claim 86, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_1-C_5-alkyl optionally substituted with one, two, three, or four substituents selected from: halogen and hydroxyl.

88. The compound according to claim 86, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: butyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, pentyl, and propyl, wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: fluoro and hydroxyl.

89. The compound according to claim 86, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 2,2-dimethylpropan-2-yl (neopentyl), 2-methylpropyl (isobutyl), butyl, ethyl, ethyl-d_5, methyl, methyl-d_3, pentyl, propan-2-yl (isopropyl), and propyl; wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: fluoro and hydroxyl.

90. The compound according to claim 86, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 1,1,1-trifluoropropan-2-yl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, propan-2-yl, and propyl.

91. The compound according to claim 86, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 1,1,1-trifluoropropan-2-yl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, propan-2-yl, and propyl.

92. The compound according to claim 86, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, 1,1,1-trifluoropropan-2-yl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoro-2-methylpropyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, propan-2-yl, and propyl.

93. The compound according to claim 86, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-2-hydroxypropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, 1,1,1-trifluoropropan-2-yl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, ethyl, ethyl-d_5, fluoromethyl, methyl, methyl-d_3, propan-2-yl, and propyl.

94. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_3-C_7-cycloalkyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

95. The compound according to claim 94, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_3-C_4-cycloalkyl optionally substituted with one or two substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, and halogen.

96. The compound according to claim 94, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: cyclobutyl and cyclopropyl; wherein each R^1 group is optionally substituted with one or two substituents selected from: fluoro, methoxy, methyl, and trifluoromethyl.

97. The compound according to claim 94, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 3,3-dimethylcyclobutyl, 1-methylcyclobutyl, 3-(trifluoromethyl)cyclobutyl, 3,3-difluorocyclobutyl, 3-fluorocyclobutyl, 3-methoxycyclobutyl, cyclobutyl, and cyclopropyl.

98. The compound according to claim 94, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 3,3-dimethylcyclobutyl, 3-(trifluoromethyl)cyclobutyl, 3,3-difluorocyclobutyl, 3-fluorocyclobutyl, 3-methoxycyclobutyl, cyclobutyl, and cyclopropyl.

99. The compound according to claim 94, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, 1-methylcyclobutyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, cyclobutyl, and cyclopropyl.

100. The compound according to claim 94, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, cyclobutyl, and cyclopropyl.

101. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_3-C_7-cycloalkyl-C_1-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

102. The compound according to claim 101, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_3-C_5-cycloalkyl-C_1-C_2-alkylene optionally substituted with one, two, or three substituents selected from: C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

103. The compound according to claim 101, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, and cyclobutylmethyl; wherein each R^1 group is optionally substituted with one or two substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, and methyl.

104. The compound according to claim 101, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 1-cyclobutylethyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, and 1-cyclobutylethyl.

105. The compound according to claim 101, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-cyanocyclopropyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*R*)-1-cyclobutylethyl, (1*S*)-1-cyclobutylethyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl,

(2-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, and [(1*S*)-2,2-dimethylcyclopropyl]methyl.

106. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

107. The compound according to claim 106, or a pharmaceutically acceptable salt thereof, wherein R^1 is (cyclopropoxy)ethyl.

108. The compound according to claim 106, or a pharmaceutically acceptable salt thereof, wherein R^1 is 2-cyclopropoxyethyl.

109. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_4-C_8-bicycloalkyl-C_1-C_4-alkylene optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

110. The compound according to claim 109, or a pharmaceutically acceptable salt thereof, wherein R^1 is (C_4-C_5-bicycloalkyl)CH_2.

111. The compound according to claim 109, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl and (bicyclo[2.1.1]hexanyl)methyl.

112. The compound according to claim 109, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentan-1-yl)methyl, and (bicyclo[2.1.1]hexan-1-yl)methyl.

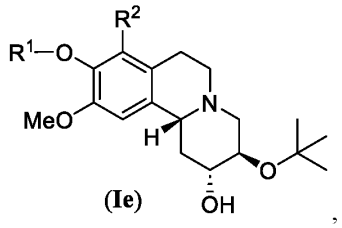
113. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_5-C_{11}-spiro-cycloalkyl optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

114. The compound according to claim 113, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_7-spiro-cycloalkyl.

115. The compound according to claim 113, or a pharmaceutically acceptable salt thereof, wherein R^1 is spiro[3.3]heptanyl.

116. The compound according to claim 113, or a pharmaceutically acceptable salt thereof, wherein: R^1 is spiro[3.3]heptan-2-yl.

117. The compound of claim 1, wherein the compound is of Formula (**Ie**):



(**Ie**),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl; and

R^2 is selected from: F, Cl, and Br.

118. The compound according to claim 117, or a pharmaceutically acceptable salt thereof, wherein R^2 is F.

119. The compound according to claim 117, or a pharmaceutically acceptable salt thereof, wherein R^2 is Cl.

120. The compound according to claim 117, or a pharmaceutically acceptable salt thereof, wherein R^2 is Br.

121. The compound according to any one of claims 117 to 120, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, and C_5-C_{11}-spiro-cycloalkyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-alkoxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, halogen, and hydroxyl.

122. The compound according to any one of claims 117 to 121, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

123. The compound according to any one of claims 117 to 122, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (bicyclo[1.1.1]pentanyl)methyl, (bicyclo[2.1.1]hexanyl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropoxy)ethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, (oxetanyl)methyl, butyl, cyclobutyl, cyclopropyl, dimethylpropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, methylpropyl, oxetanyl, pentyl, propyl, and spiro[3.3]heptanyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

124. The compound according to any one of claims 117 to 123, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

125. The compound according to any one of claims 117 to 124, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopentyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2,2-

dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, pentyl, propan-2-yl (isopropyl), propyl, and spiro[3.3]heptan-2-yl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: cyano, difluoromethyl, fluoro, hydroxyl, methoxy, methyl, and trifluoromethyl.

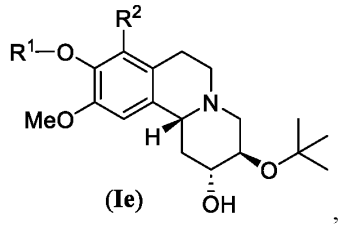
126. The compound according to any one of claims 117 to 125, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2,2-dimethylcyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-2-yl)methyl, (oxetan-3-yl)methyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-fluoropropyl, 2-hydroxy-2-methylpropyl, 2-hydroxypropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluorocyclobutyl, 3-fluoropropyl, 3-methoxycyclobutyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

127. The compound according to any one of claims 117 to 126, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ((2*R*)-oxetan-2-yl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*r*,3*r*)-3-methoxycyclobutan-1-yl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-methoxycyclobutan-1-yl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-2-hydroxypropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-

yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (oxetan-3-yl)methyl, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-cyclopropoxyethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl, 2-methoxyethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, oxetan-3-yl, propan-2-yl, propyl, and spiro[3.3]heptan-2-yl.

128. The compound according to any one of claims 117 to 127, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-cyanocyclobutyl)methyl, (1-fluorocyclobutyl)methyl, (1-fluorocyclopropyl)methyl, (1-hydroxycyclobutyl)methyl, (1-methylcyclopropyl)methyl, (1r,3r)-3-(trifluoromethyl)cyclobutyl, (1*r*,3*r*)-3-fluorocyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-fluorocyclobutyl, (2,2-difluoro-3-methylcyclopropyl)methyl, (2,2-difluorocyclobutyl)methyl, (2,2-difluorocyclopentyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2*R*)-2-fluoropropyl, (2*R*)-3,3,3-trifluoro-2-hydroxypropyl, (2*S*)-2-2-fluoropropyl, (3,3-difluorocyclobutyl)methyl, (3,3-difluorocyclopentyl)methyl, (3-fluorooxetan-3-yl)methyl, (bicyclo[1.1.1]pentan-1-yl)methyl, (bicyclo[2.1.1]hexan-1-yl)methyl, (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, [(1*R*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-difluorocyclopropyl]methyl, [(1*S*)-2,2-dimethylcyclopropyl]methyl, 2-(trifluoromethoxy)ethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2,2-dimethylpropan-2-yl (neopentyl), 2-fluoroethyl, 2-methylpropyl (isobutyl), 3,3,3-trifluoropropyl, 3,3-difluorocyclobutyl, 3,3-dimethylcyclobutyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, butan-1-yl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, propyl, and spiro[3.3]heptan-2-yl.

129. The compound of claim 1, wherein the compound is of Formula (**Ie**):



(**Ie**),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, and C_3-C_7-cycloalkyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-haloalkyl, halogen, and hydroxyl; and

R^2 is selected from: F, Cl, and Br.

130. The compound according to claim 129, or a pharmaceutically acceptable salt thereof, wherein R^2 is F.

131. The compound according to claim 129, or a pharmaceutically acceptable salt thereof, wherein R^2 is Cl.

132. The compound according to claim 129, or a pharmaceutically acceptable salt thereof, wherein R^2 is Br.

133. The compound according to any one of claims 129 to 132, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, and C_3-C_7-cycloalkyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: C_1-C_4-haloalkyl, halogen, and hydroxyl.

134. The compound according to any one of claims 129 to 133, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: difluoromethyl, fluoro, hydroxyl, and trifluoromethyl.

135. The compound according to any one of claims 129 to 134, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, (methoxy)ethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: difluoromethyl, fluoro, hydroxyl, and trifluoromethyl.

136. The compound according to any one of claims 129 to 135, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl,

(cyclopropyl)methyl-d_2, 2-methoxyethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: difluoromethyl, fluoro, hydroxyl, and trifluoromethyl.

137. The compound according to any one of claims 129 to 136, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, 2-methoxyethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: difluoromethyl, fluoro, hydroxyl, and trifluoromethyl.

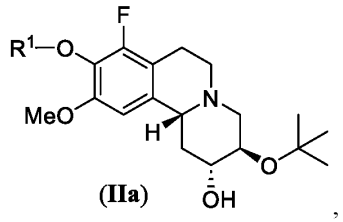
138. The compound according to any one of claims 129 to 137, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-fluorocyclopropyl)methyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2-fluoroethyl, 2-fluoropropyl, 2-methoxyethyl, 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoro-2-hydroxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, and propan-2-yl.

139. The compound according to any one of claims 129 to 138, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-fluorocyclopropyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2*R*)-2-fluoropropyl, (2*S*)-3,3,3-trifluoro-2-hydroxypropyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, [(1*S*)-2,2-difluorocyclopropyl]methyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 2-fluoroethyl, 2-methoxyethyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, and propan-2-yl.

140. The compound according to any one of claims 129 to 139, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-(difluoromethyl)cyclopropyl)methyl, (1-fluorocyclopropyl)methyl, (1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (2,2-difluorocyclopropyl)methyl, (2-fluorocyclopropyl)methyl, (2*R*)-2-fluoropropyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, [(1*S*)-2,2-difluorocyclopropyl]methyl, 2,2,2-trifluoroethyl, 2,2-

difluoroethyl, 2,2-difluoropropyl, 2-fluoroethyl, 3,3,3-trifluoropropyl, 3-fluoropropyl, 4,4,4-trifluorobutyl, cyclopropyl, ethyl, and ethyl-d_5.

141. The compound of claim 1, wherein the compound is of Formula **(IIa)**:



(IIa),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: C_1-C_6-alkyl, C_3-C_7-cycloalkyl, and C_3-C_7-cycloalkyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: C_1-C_4-haloalkyl and halogen.

142. The compound according to claim 141, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: C_1-C_6-alkyl, C_3-C_7-cycloalkyl, and C_3-C_7-cycloalkyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one, two, or three substituents selected from: C_1-C_4-haloalkyl and halogen.

143. The compound according to claim 141 or 142, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, cyclobutyl, cyclopropyl, ethyl, and propyl;

wherein each R^1 group is optionally substituted with one or more substituents selected from: fluoro and trifluoromethyl.

144. The compound according to any one of claims 141 to 143, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, 2-methoxyethyl, butyl, cyclobutyl, cyclopropyl, ethyl, ethyl-d_5, methyl, methyl-d_3, propan-2-yl (isopropyl), and propyl;

wherein each R^1 group is optionally substituted with one, two, three, or four substituents selected from: fluoro and trifluoromethyl.

145. The compound according to any one of claims 141 to 144, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-fluorocyclopropyl)methyl, (2,2-

difluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl-d_2, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 3-(trifluoromethyl)cyclobutyl, 3,3,3-trifluoropropyl, and cyclopropyl.

146. The compound according to any one of claims 141 to 145, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-fluorocyclopropyl)methyl, (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl-d_2, [(1*S*)-2,2-difluorocyclopropyl]methyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, and cyclopropyl.

147. The compound according to claim 141 or 142, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from C_1-C_6-alkyl optionally substituted with one, two, or three substituents selected from halogen.

148. The compound according to claim 147, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: ethyl and propyl; wherein each R^1 group is optionally substituted with one, two, or three substituents selected from fluoro.

149. The compound according to claim 147, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2-difluoropropyl, and 3,3,3-trifluoropropyl.

150. The compound according to claim 141 or 142, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from C_3-C_7-cycloalkyl optionally substituted with one substituent selected from C_1-C_4-haloalkyl.

151. The compound according to claim 150, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: cyclobutyl and cyclopropyl; wherein each R^1 group is optionally substituted with one substituent selected from trifluoromethyl.

152. The compound according to claim 150, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: cyclopropyl and 3-(trifluoromethyl)cyclobutyl.

153. The compound according to claim 150, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: cyclopropyl and (1*s*,3*s*)-3-(trifluoromethyl)cyclobutyl.

154. The compound according to claim 141 or 142, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from C_3-C_7-cycloalkyl-C_1-C_4-alkylene optionally substituted with one or two, substituents selected from halogen.

155. The compound according to claim 154, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (cyclobutyl)methyl, (cyclopropyl)methyl, and (cyclopropyl)methyl-d_2; wherein each R^1 group is optionally substituted with one or two substituents selected from fluoro.

156. The compound according to claim 154, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-fluorocyclopropyl)methyl, (2,2-difluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, and (cyclopropyl)methyl-d_2.

157. The compound according to claim 154, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from: (1-fluorocyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, and [(1*S*)-2,2-difluorocyclopropyl]methyl.

158. The compound according to claim 1, selected from the following compounds:

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*R*)-2-fluoropropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 1**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*S*)-2-fluoropropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 2**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(1*S*)-1-cyclobutylethoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 3**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(1*R*)-1-cyclobutylethoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 4**);

trans-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluoro-3-methylcyclopropyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 5**);

cis-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 6**);

trans-(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 7**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(3,3-dimethylcyclobutoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 8**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-methoxycyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 9**);

(2*R*,3*R*,11b*R*)-9-{bicyclo[1.1.1]pentan-1-ylmethoxy}-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 10**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1-methylcyclopropyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 11**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-dimethylcyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 12**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-methoxycyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 13**);

(2*R*,3*R*,11b*R*)-9-{bicyclo[2.1.1]hexan-1-ylmethoxy}-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 14**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(1-methylcyclobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 15**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*R*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 16**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-fluorocyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 17**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-fluorocyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 18**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-{spiro[3.3]heptan-2-yloxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 19**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(3,3-difluorocyclobutoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 20**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 21**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 22**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 23**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 24**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1,1,1-trifluoropropan-2-yl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 25**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[2-(trifluoromethoxy)ethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 26**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(4,4,4-trifluorobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 27**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 28**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 29**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 30**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 31**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 32**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-hydroxy-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 33**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 34**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 35**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 36**);

1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile (**Compound 37**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclopentyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 38**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 39**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 40**);

(2*R*,3*R*,11b*R*)-9-butoxy-3-(*tert*-butoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 41**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 42**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 43**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 44**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(3-fluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 45**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-fluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 46**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2-cyclopropoxyethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 47**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclobutoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 48**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-($^2H_5$)ethoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 49**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-{2-oxabicyclo[2.1.1]hexan-4-ylmethoxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 50**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(fluoromethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 51**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 52**);

1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclopropane-1-carbonitrile (**Compound 53**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 54**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(3-fluorooxetan-3-yl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 55**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 56**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 57**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 58**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 59**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 60**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopentyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 61**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-dimethylpropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 62**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 63**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 64**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 65**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 66**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 67**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 68**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-ethoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 69**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclopropoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 70**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(cyclopropylmethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 71**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopropyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 72**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(cyclobutylmethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 73**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-($^2H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 74**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 75**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 76**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 77**);

1-({[(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile (**Compound 78**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(3,3-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 79**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 80**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-($^2H_5$)ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 81**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[cyclopropyl($^2H_2$)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 82**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 83**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2,2-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 84**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 85**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(3,3-difluorocyclobutoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 86**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 87**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 88**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 89**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-cyclobutoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 90**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2,2-difluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 91**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(cyclopropylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 92**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-cyclopropoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 93**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 94**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(3,3-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 95**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 96**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 97**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 98**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 99**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 100**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 101**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 102**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 103**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 104**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 105**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(3*S*)-oxolan-3-yloxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 106**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 107**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 108**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-[(3*R*)-oxolan-3-yloxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 109**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 110**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-(2-cyclopropoxyethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 111**);

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-chloro-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 112**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-propoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 113**);

(2*R*,3*R*,11b*R*)-8-bromo-9-butoxy-3-(*tert*-butoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 114**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(propan-2-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 115**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(cyclobutylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 116**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(oxetan-3-yloxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 117**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2-methoxyethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 118**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 119**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(3-fluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 120**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-fluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 121**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(cyclopropylmethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 122**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 123**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 124**);

1-({[(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclopropane-1-carbonitrile (**Compound 125**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-cyclobutoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 126**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 127**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 128**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-{2-oxabicyclo[2.1.1]hexan-4-ylmethoxy}-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 129**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-cyclopropoxyethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 130**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^2H_5$)ethoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 131**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(fluoromethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 132**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2,2-difluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 133**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-fluorocyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 134**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-dimethylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 135**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3-fluorooxetan-3-yl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 136**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(oxetan-3-ylmethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 137**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*S*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 138**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*R*)-oxetan-2-ylmethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 139**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[cyclopropyl($^2H_2$)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 140**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2-methylpropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 141**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(5,5,5-trifluoropentyl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 142**);

1-({[(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-2-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-9-yl]oxy}methyl)cyclobutane-1-carbonitrile (**Compound 143**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(3,3-difluorocyclopentyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 144**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-{[1-(difluoromethyl)cyclopropyl]methoxy}-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 145**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-fluoro-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 146**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 147**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(3,3-difluorocyclobutoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 148**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(1-hydroxycyclobutyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 149**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 150**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1-methylcyclobutyl)methoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 151**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 152**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 153**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 154**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(1,1,1-trifluoropropan-2-yl)oxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 155**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[2-(trifluoromethoxy)ethoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 156**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-(4,4,4-trifluorobutoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 157**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 158**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-cyclopropoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 159**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*R*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 160**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-10-methoxy-9-[(2*S*)-3,3,3-trifluoro-2-hydroxypropoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 161**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2*S*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol (**Compound 162**);

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-[(2*R*)-2-hydroxypropoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 163)**;

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-(2-hydroxy-2-methylpropoxy)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 164)**;

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9,10-dimethoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 165)**; and

(2*R*,3*R*,11b*R*)-8-bromo-3-(*tert*-butoxy)-9-($^{2}H_3$)methoxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 166)**;

or a pharmaceutically acceptable salt thereof.

159. The compound according to claim 1, selected from the following compounds:

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-{[(1*S*)-2,2-difluorocyclopropyl]methoxy}-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 21)**;

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(2,2,2-trifluoroethoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 22)**;

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-(3,3,3-trifluoropropoxy)-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 23)**;

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoropropoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 24)**;

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-(2,2-difluoroethoxy)-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 28)**;

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-9-[(1-fluorocyclopropyl)methoxy]-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 52)**;

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[(3,3-difluorocyclobutyl)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 54)**;

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-8-fluoro-10-methoxy-9-[(1*s*,3*s*)-3-(trifluoromethyl)cyclobutoxy]-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 66)**;

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-[cyclopropyl($^{2}H_2$)methoxy]-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 68)**; and

(2*R*,3*R*,11b*R*)-3-(*tert*-butoxy)-9-cyclopropoxy-8-fluoro-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-ol **(Compound 70)**;

or a pharmaceutically acceptable salt thereof.

160. A pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising the compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof.

161. A pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising the compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

162. A pharmaceutical composition comprising the compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

163. A method for preparing a pharmaceutical composition comprising the step of admixing a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

164. A method of treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162.

165. A method of treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; wherein the VMAT2 disease or disorder is selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington's disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson's/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

166. A method of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162.

167. A method of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; wherein the neurological or psychiatric disease or disorder is selected from: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis.

168. A method of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.

169. A method of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; wherein the hyperkinetic movement disorder is selected from: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.

170. A method of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; wherein the hyperkinetic movement disorder is tardive dyskinesia.

171. A method of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; wherein the hyperkinetic movement disorder is Huntington's disease.

172. A method of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.

173. The method according to claim 165 or 166; wherein the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder.

174. The method according to claim 165 or 166; wherein the neurological or psychiatric disease or disorder is schizophrenia.

175. The method according to claim 165 or 166; wherein the neurological or psychiatric disease or disorder is schizoaffective disorder.

176. The method according to claim 165 or 166; wherein the neurological or psychiatric disease or disorder is obsessive-compulsive disorder.

177. The method according to claim 165 or 166; wherein the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder.

178. The method according to claim 165 or 166; wherein the neurological or psychiatric disease or disorder is autism spectrum disorder.

179. The method according to any one of claims 164 to 178, wherein the method comprises using the compound, salt, product, or composition in adjunctive therapy.

180. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder.

181. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a

dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington's disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson's/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

182. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder.

183. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder selected from: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis.

184. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating a hyperkinetic movement disorder.

185. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating a hyperkinetic movement disorder; wherein the hyperkinetic movement disorder is selected from: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.

186. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating tardive dyskinesia.

187. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating Huntington's disease.

188. Use of a compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof, a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; in the manufacture of a medicament for treating chorea associated with Huntington's disease.

189. The use according to claim 180 or 181, wherein the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder.

190. The use according to claim 180 or 181; wherein the neurological or psychiatric disease or disorder is schizophrenia.

191. The use according to claim 180 or 181; wherein the neurological or psychiatric disease or disorder is schizoaffective disorder.

192. The use according to claim 180 or 181; wherein the neurological or psychiatric disease or disorder is obsessive-compulsive disorder.

193. The use according to claim 180 or 181; wherein the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder.

194. The use according to claim 180 or 181; wherein the neurological or psychiatric disease or disorder is autism spectrum disorder.

195. The use of the compound, salt, product, or composition according to any one of claims 180 to 194, wherein treating comprises using the compound, salt, product, or composition in adjunctive therapy.

196. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method of treatment of the human or animal body by therapy.

197. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder.

198. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington's disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson's/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

199. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating a neurological or psychiatric disease or disorder.

200. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating a neurological or psychiatric disease or disorder selected from: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis.

201. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating a hyperkinetic movement disorder.

202. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating a hyperkinetic movement disorder; wherein the hyperkinetic movement disorder is selected from: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.

203. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating tardive dyskinesia.

204. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating Huntington's disease.

205. A compound according to any one of claims 1 to 159, or a pharmaceutically acceptable salt thereof; a pharmaceutical product according to claim 160 or 161; or a pharmaceutical composition according to claim 162; for use in a method for treating chorea associated with Huntington's disease.

206. The compound, salt, product, or composition for use according to claim 198 or 199, wherein the neurological or psychiatric disease or disorder is selected from: schizophrenia and schizoaffective disorder.

207. The compound, salt, product, or composition for use according to claim 198 or 199, wherein the neurological or psychiatric disease or disorder is schizophrenia.

208. The compound, salt, product, or composition for use according to claim 198 or 199, wherein the neurological or psychiatric disease or disorder is schizoaffective disorder.

209. The compound, salt, product, or composition for use according to claim 198 or 199, wherein the neurological or psychiatric disease or disorder is obsessive-compulsive disorder.

210. The compound, salt, product, or composition for use according to claim 198 or 199, wherein the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder.

211. The compound, salt, product, or composition for use according to claim 198 or 199, wherein the neurological or psychiatric disease or disorder is autism spectrum disorder.

212. The compound, salt, product, or composition for use according to any one of claims 196 to 211, wherein the method for treating comprises using the compound, salt, product, or composition in adjunctive therapy.