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**LISA A. BONNER ET AL: "Mapping the Catechol Binding Site in Dopamine D1 Receptors: Synthesis and Evaluation of Two Parallel Series of Bicyclic Dopamine Analogues", CHEMMEDCHEM, vol. 6, no. 6, 6 June 2011 (2011-06-06), DE, pages 1024 - 1040, XP055666214, ISSN: 1860-7179, DOI: 10.1002/cmdc.201100010**  
**BRUNO MACCHIA ET AL: "Conformationally restrained analogs of sympathomimetic catecholamines.**

Fortsættes ...

Synthesis, conformational analysis and adrenergic activity of isochroman derivatives", JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 21, 1 October 1993 (1993-10-01), US, pages 3077 - 3086, XP055666381, ISSN: 0022-2623, DOI: 10.1021/jm00073a006

DE NINNO M P ET AL: "SYNTHESIS AND DOPAMINERGIC ACTIVITY OF 3-SUBSTITUTED 1-(AMINOMETHYL)-3,4-DIHYDRO-5,6-DIHYDROXY-1H-2-BENZOPYRANS: CHARACTERIZATION OF AN AUXILIARY BINDING REGION IN THE D1 RECEPTOR", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 34, no. 8, 1 January 1991 (1991-01-01), pages 2561 - 2569, XP002528845, ISSN: 0022-2623, DOI: 10.1021/JM00112A034

DATABASE CAPLUS [online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; NOZAWA, TATSUTSUGU ET AL: "Benzopyran derivatives as inhibitors for the formation of active oxygen", XP002797488, retrieved from STN Database accession no. 1989:553630

NOZAWA, TATSUTSUGU ET AL: "Benzopyran derivatives as inhibitors for the formation of active oxygen", JPN. KOKAI TOKKYO KOHO, 12 PP. CODEN: JKXXAF, 1989

DATABASE CAPLUS [online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KUMAR, ASHOK ET AL: "Catecholamines in a semi-rigid framework: synthesis and biological activities of N-substituted 1-aminomethyl-5,6- and 6,7-dihydroxyisochromans", XP002797489, retrieved from STN Database accession no. 1988:5769

KUMAR, ASHOK ET AL: "Catecholamines in a semi-rigid framework: synthesis and biological activities of N-substituted 1-aminomethyl-5,6- and 6,7-dihydroxyisochromans", INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY , 26B(1), 47-51 CODEN: IJSBDB; ISSN: 0376-4699, 1987

VITO CAPRIATI ET AL: "Directed Ortho Lithiation of N -Alkylphenylaziridines", ORGANIC LETTERS, vol. 7, no. 17, 1 August 2005 (2005-08-01), US, pages 3749 - 3752, XP055666219, ISSN: 1523-7060, DOI: 10.1021/o10514121

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# DESCRIPTION

## Description

### FIELD OF THE INVENTION

**[0001]** The invention relates to 1-aminomethylisochroman compounds, and pharmaceutical compositions containing them, for the treatment of central nervous system diseases and disorders. Such diseases and disorders include depression, bipolar disorder, pain, schizophrenia, obsessive compulsive disorder, psychostimulation, addiction, social disorder, attention deficit hyperactivity disorder, an anxiety disorder, autism, a cognitive impairment, or a neuropsychiatric symptom such as apathy, depression, anxiety, cognitive impairment, psychosis, aggression, agitation, impulse control, and sleep disruption in neurological diseases such as Alzheimer's and Parkinson's diseases.

### BACKGROUND OF THE INVENTION

**[0002]** Central nervous system diseases and disorders affect a wide range of the population with differing severity. Neurological and psychiatric diseases and disorders include major depression, schizophrenia, bipolar disorder, obsessive compulsive disorder (OCD), panic disorder, and posttraumatic stress disorder (PTSD), among others. These diseases and disorders affect a person's thoughts, mood, behavior and social interactions and can significantly impair daily functioning. See, e.g., Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., American Psychiatric Association (2000) ("DSM-IV-TR"); Diagnostic and Statistical Manual of Mental Disorders, 5th Ed., American Psychiatric Association (2013) ("DSM-5"). Furthermore, neuropsychiatric symptoms such as apathy, depression, anxiety, cognitive impairment, psychosis, aggression, agitation, impulse control and sleep disruption are now recognized as core impairments of neurological diseases and disorders such as Alzheimer's and Parkinson's diseases.

**[0003]** While medications exist for some aspects of these diseases, there remains a need for effective treatments for various neurological and psychiatric diseases and disorders. For example, while mood stabilizers such as lithium and valproate, antidepressants and antipsychotic drugs are used to treat mood disorders, more effective medications are necessary. And current antipsychotics may be successful in treating the positive symptoms of schizophrenia but fare less well for the negative and cognitive symptoms. Additionally, current antidepressants are typically effective only for a proportion of subjects suffering from depression. Furthermore, despite the fact that the behavioral and psychiatric symptoms of

neurological disease such as Parkinson's disease and Alzheimer's disease are major reasons for the institutionalization of subjects, few drugs exist to treat them.

US4021451 relates to a process applicable to the preparation of a wide variety of novel polycyclic heterocycles having a newly-formed pyran ring. The new heterocycles are said to be useful for preparing derivatives having anti-inflammatory, antibacterial or antifungal activities.

DE2624693 relates to isochroman derivatives and a process for their production.

GB1552004 relates to isochroman derivatives.

JPH0570453A relates to an aminomethylisochroman derivative expressed by a formula defined therein, which are said to have powerful antagonistic action on thromboxane A2 and be useful for treating thrombosis, thromboembolism and ischemia or as antiasthmatic and antiallergic agents.

WO9638435A1 relates to novel compounds having a formula defined therein and pharmaceutically acceptable salts, esters and amides thereof. The compounds are said to be useful for treating dopamine-related neurological, psychological and cardiovascular disorders as well as in the treatment of cognitive impairment, attention deficit disorder, and substance abuse and other addictive behavior disorders.

WO2005111025A1 relates to compounds of a formula defined therein, a stereoisomer or a pharmaceutically acceptable salt thereof, as well as a method for treating dopamine-related neurological disorders selected from the group consisting of neurological, psychological, cardiovascular, cognitive or attention disorders, substance abuse and addictive behavior, or a combination thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of the disclosed compounds.

WO2011069063A2 relates to multicyclic compounds, methods of their synthesis, pharmaceutical compositions comprising the compounds, and methods of their use. The compounds are said to be provided for use in the treatment, prevention and/or management of various neurological disorders, including but not limited to psychosis and schizophrenia.

LISA A. BONNER ET AL, "Mapping the Catechol Binding Site in Dopamine D1 Receptors: Synthesis and Evaluation of Two Parallel Series of Bicyclic Dopamine Analogues", CHEMMEDCHEM, DE, (20110606), vol. 6, no. 6, pages 1024-1040, relates to a novel class of isochroman dopamine analogues, said to have >100-fold selectivity for D<sub>1</sub>-like over D<sub>2</sub>-like receptors.

BRUNO MACCHIA ET AL, "Conformationally restrained analogs of sympathomimetic catecholamines. Synthesis, conformational analysis and adrenergic activity of isochroman derivatives", JOURNAL OF MEDICINAL CHEMISTRY, US, (19931001), vol. 36, no. 21, pages 3077-3086, relates to conformationally restrained analogs of sympathomimetic catecholamines.

DA NINNO M P ET AL, "Synthesis and dopaminergic activity of 3-substituted 1-

(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1H-2-benzopyrans: Characterization of an auxiliary binding region in the D1 receptor", Journal of Medicinal Chemistry, American Chemical Society, US, (19910101), vol. 34, no. 8, pages 2561-2569, relates to the synthesis and dopaminergic activity of 3-substituted 1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1H-2-benzopyrans.

NOZAWA, TATSUTSUGU ET AL, "Benzopyran derivatives as inhibitors for the formation of active oxygen", CAPLUS, CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, relates to benzopyran derivatives as inhibitors for the formation of active oxygen.

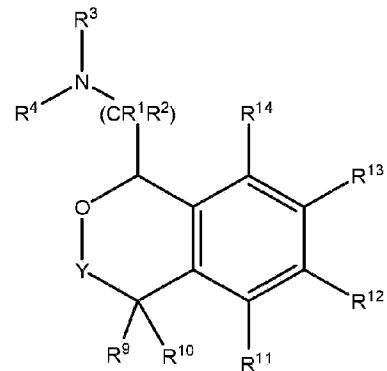
KUWAR, ASHOK ET AL, "Catecholamines in a semi-rigid framework: synthesis and biological activities of N-substituted 1-aminomethyl-5,6- and 6,7-dihydroxyisochromans", CAPLUS, CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, relates to N-substituted 1-aminomethyl-5,6- and 6,7-dihydroxyisochromans.

US3438995 relates to diazaheterocyclic substituted benzoheterocyclic compounds, namely isochromans, phthalans and the corresponding thio compounds substituted at the 1-position by a 2-imidazolyl, 2-tetrahydropyrimidinyl, or 2-tetrahydrodiazepinyl group. The compounds are said to be useful as rubber accelerators, anti-oxidants, corrosion inhibitors, central nervous system depressants and anti-inflammatories.

US4500543 relates to 1-aminomethyl-phthalans represented by a formula defined therein and pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions comprising the compounds and a pharmaceutically acceptable carrier or diluent.

## SUMMARY OF THE INVENTION

**[0004]** The invention is defined by the appended claims. In particular, the invention relates to a compound of formula I:



or a pharmaceutically acceptable salt thereof,  
wherein:

Y is  $-C(R^5R^6)-$ ;

$R^1$  and  $R^2$  are chosen independently from H, aliphatic ( $C_1-C_8$ )hydrocarbon and ( $C_3-C_8$ )

$C_6$ cycloalkyl, wherein the aliphatic ( $C_1$ - $C_8$ )hydrocarbon is optionally substituted with one or more of halogen, hydroxyl, ( $C_1$ - $C_6$ )alkoxy, amino, ( $C_1$ - $C_6$ )alkylamino and di( $C_1$ - $C_6$ )alkylamino;

or, taken together,  $R^1$  and  $R^2$  may form ( $C_3$ - $C_6$ )cycloalkyl;

$R^3$  is hydrogen and  $R^4$  is hydrogen or methyl;

$R^5$  and  $R^6$  are both hydrogen;

$R^9$  and  $R^{10}$  are chosen independently from H, halogen, hydroxyl, ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )haloalkyl and ( $C_1$ - $C_6$ )alkoxy;

$R^{11}$ ,  $R^{12}$ ,  $R^{13}$ , and  $R^{14}$  are chosen independently from H, fluoro, chloro, iodo, cyano, and aliphatic ( $C_1$ - $C_8$ )hydrocarbon,

with the proviso that at least one of  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ , and  $R^{14}$  is other than hydrogen.

**[0005]** In another aspect, the invention relates to a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

**[0006]** In another aspect, the invention relates to a compound of the invention, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the invention, for use in a method for treating a neurological or psychiatric disease or disorder in a subject in need thereof.

#### BRIEF DESCRIPTION OF THE DRAWINGS

#### [0007]

Figures 1a and 1b show the effects of a reference compound (not of the invention) and a representative compound of the invention, respectively, on mice in a forced swim test.

Figures 2a to 2b show the effects of a reference compound (not of the invention) and a representative compound of the invention, respectively, on inhibition of PCP-induced HLA.

Figure 3a shows the effect of a reference compound (not of the invention), on mice in an amphetamine-induced hyperlocomotion assay and Figures 3b to 3d show the effects of representative compounds of the invention, on mice in an amphetamine-induced hyperlocomotion assay.

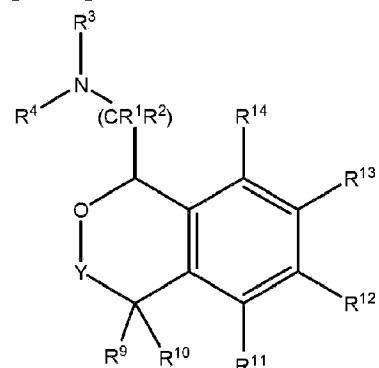
Figures 4a to 4c show the effects of representative compounds of the invention on mice in a

mouse tail suspension test.

#### DETAILED DESCRIPTION

**[0008]** The invention is defined by the appended claims. The compounds or compositions of the invention are disclosed herein for use in methods of treating neurological or psychiatric diseases, disorders or impairments. In some embodiments, the neurological or psychiatric disease or disorder is depression, bipolar disorder, pain, schizophrenia, obsessive compulsive disorder, psychostimulation, addiction, social disorder, attention deficit hyperactivity disorder, an anxiety disorder, a movement disorder, epilepsy, autism, Alzheimer's disease, Parkinson's disease or cognitive impairments. In one embodiment, the disease or disorder is depression, particularly treatment-resistant depression (TRD), major depressive disorder (MDD), unipolar depression, bipolar depression or depression associated with another disease or disorder. In some embodiments, the impairments in neurological diseases or disorders such as Alzheimer's and Parkinson's diseases include neuropsychiatric symptoms such as apathy, depression, anxiety, cognitive impairment, psychosis, aggression, agitation, impulse control disorders, and/or sleep disorders.

**[0009]** The invention relates to compounds of formula I:



**I**

or a pharmaceutically acceptable salt thereof,

wherein:

Y is  $-\text{C}(\text{R}^5\text{R}^6)-$ ;

$\text{R}^1$  and  $\text{R}^2$  are chosen independently from H, aliphatic ( $\text{C}_1\text{-C}_8$ )hydrocarbon and ( $\text{C}_3\text{-C}_6$ )cycloalkyl, wherein the aliphatic ( $\text{C}_1\text{-C}_8$ )hydrocarbon is optionally substituted with one or more of halogen, hydroxyl, ( $\text{C}_1\text{-C}_6$ )alkoxy, amino, ( $\text{C}_1\text{-C}_6$ )alkylamino and di( $\text{C}_1\text{-C}_6$ )alkylamino;

or, taken together,  $\text{R}^1$  and  $\text{R}^2$  may form ( $\text{C}_3\text{-C}_6$ )cycloalkyl;

$R^3$  is hydrogen and  $R^4$  is hydrogen or methyl

$R^5$  and  $R^6$  are both hydrogen;

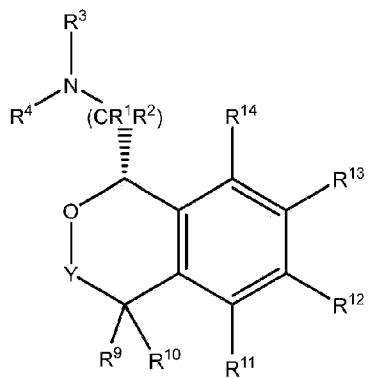
$R^9$  and  $R^{10}$  are chosen independently from H, halogen, hydroxyl, ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )haloalkyl and ( $C_1$ - $C_6$ )alkoxy;

$R^{11}$ ,  $R^{12}$ ,  $R^{13}$ , and  $R^{14}$  are chosen independently from H, fluoro, chloro, iodo, cyano, and aliphatic ( $C_1$ - $C_8$ )hydrocarbon,

with the proviso that:

at least one of  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ , and  $R^{14}$  is other than hydrogen.

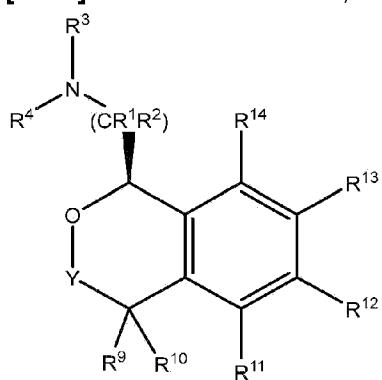
**[0010]** In one embodiment, the configuration is of formula **Ia**:



**Ia,**

or a pharmaceutically acceptable salt thereof.

**[0011]** In one embodiment, the configuration is of formula **Ib**:

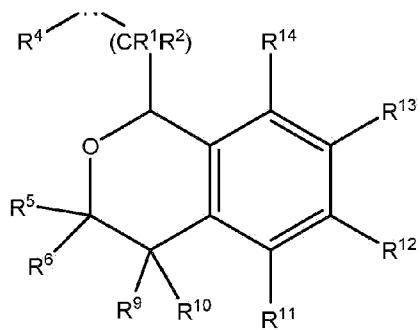


**Ib,**

or a pharmaceutically acceptable salt thereof.

**[0012]** In the invention, Y is  $-C(R^5R^6)-$ , and the compounds are of formula **II**:

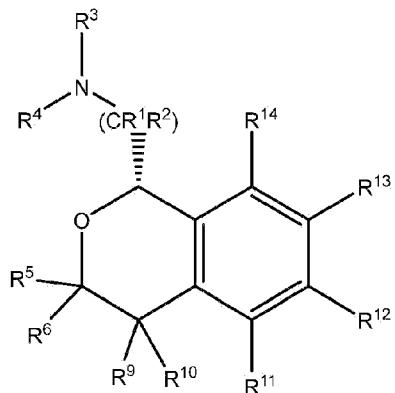




**II,**

or a pharmaceutically acceptable salt thereof.

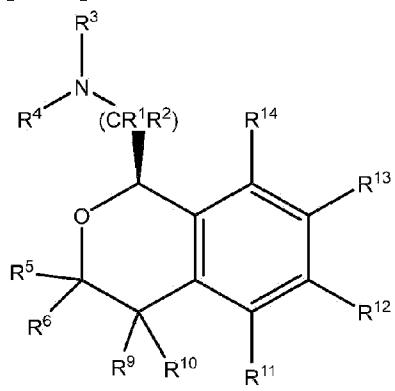
**[0013]** In one embodiment, the configuration is of formula IIa:



**IIa,**

or a pharmaceutically acceptable salt thereof.

**[0014]** In one embodiment, the configuration is of formula IIb:



**IIb,**

or a pharmaceutically acceptable salt thereof.

**[0015]** In some embodiments, R<sup>1</sup> is hydrogen. In some embodiments, R<sup>2</sup> is hydrogen or methyl.

**[0016]** In some embodiments, R<sup>3</sup> is hydrogen. In some embodiments, R<sup>4</sup> is hydrogen or

methyl.

[0017] In the invention, R<sup>5</sup> and R<sup>6</sup> are both hydrogen.

[0018] In some embodiments, R<sup>9</sup> and R<sup>10</sup> are chosen independently from H, fluoro, and methyl.

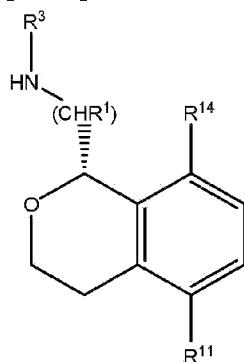
[0019] In some embodiments, R<sup>1</sup> is hydrogen; R<sup>2</sup> is hydrogen or methyl; R<sup>3</sup> is hydrogen and R<sup>4</sup> is hydrogen or methyl.

**[0020]** In some embodiments, one of  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ , and  $R^{14}$  is fluoro, chloro, methyl or cyano and the remaining three are H. In some of these embodiments,  $R^{12}$  and  $R^{13}$  are H, one of  $R^{11}$  and  $R^{14}$  is chosen from fluoro, chloro, methyl and cyano, and the other of  $R^{11}$  and  $R^{14}$  is H. In still other embodiments, two of  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ , and  $R^{14}$  are fluoro, chloro, methyl or cyano and the remaining two are H. In some of these embodiments,  $R^{12}$  and  $R^{13}$  are H, and  $R^{11}$  and  $R^{14}$  are chosen from fluoro, chloro, methyl and cyano.

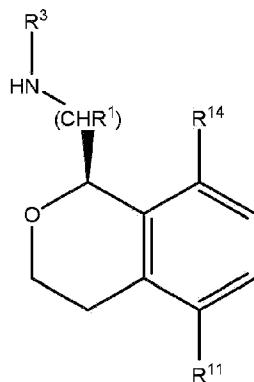
**[0021]** In some embodiments,  $R^1$  is hydrogen;  $R^2$  is hydrogen or methyl;  $R^3$  is hydrogen;  $R^4$  is hydrogen or methyl;  $R^9$  and  $R^{10}$  are hydrogen. In some of these embodiments,  $R^{12}$  and  $R^{13}$  are H, one of  $R^{11}$  and  $R^{14}$  is chosen from fluoro, chloro, methyl and cyano, and the other of  $R^{11}$  and  $R^{14}$  is H. In other of these embodiments,  $R^{12}$  and  $R^{13}$  are H, and  $R^{11}$  and  $R^{14}$  are chosen from fluoro, chloro, methyl and cyano. In some of these embodiments,  $R^{14}$  is chosen from fluoro, chloro, methyl and cyano.

**[0022]** In some embodiments, R<sup>1</sup> is hydrogen; R<sup>2</sup> is hydrogen or methyl; R<sup>3</sup> is hydrogen; R<sup>4</sup> is hydrogen or methyl; R<sup>9</sup> and R<sup>10</sup> are hydrogen; and R<sup>14</sup> is chosen from fluoro, chloro, methyl and cyano, and R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are H.

[0023] In some embodiments, C(1) of the isochroman is of absolute configuration:

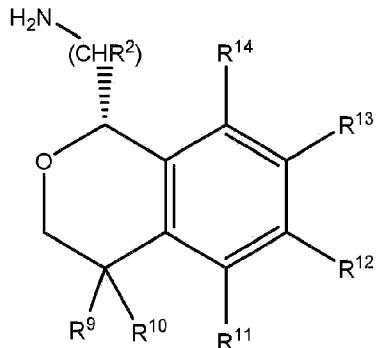


[0024] In other embodiments, C(1) of the isochroman is of absolute configuration:

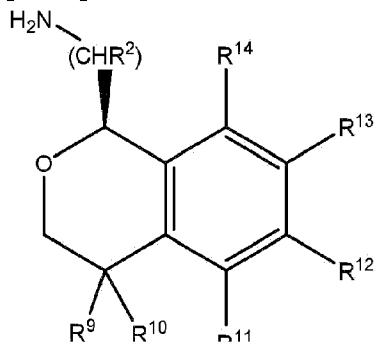


[0025] In some embodiments, R¹ is hydrogen and R² is hydrogen or methyl. In some of these embodiments, R⁴ is hydrogen; and R⁹ and R¹⁰ are each independently hydrogen, methyl or fluoro.

[0026] In some embodiments, R¹ is hydrogen; R² is hydrogen or methyl; R³ and R⁴ are both hydrogen; R⁹ and R¹⁰ are each selected from hydrogen, methyl, and fluoro; R¹¹ is hydrogen, fluoro, chloro, or methyl; and R¹² is hydrogen or fluoro. In some of these embodiments, R¹³ is hydrogen or fluoro, and R¹⁴ is selected from hydrogen, methyl, and fluoro. In some of these embodiments, R² is methyl. In some of these embodiments, R⁹ and R¹⁰ are both hydrogen. In some of these embodiments, only one of R¹¹, R¹², R¹³ and R¹⁴ is other than hydrogen. In some embodiments, C(1) of the isochroman is of absolute configuration:

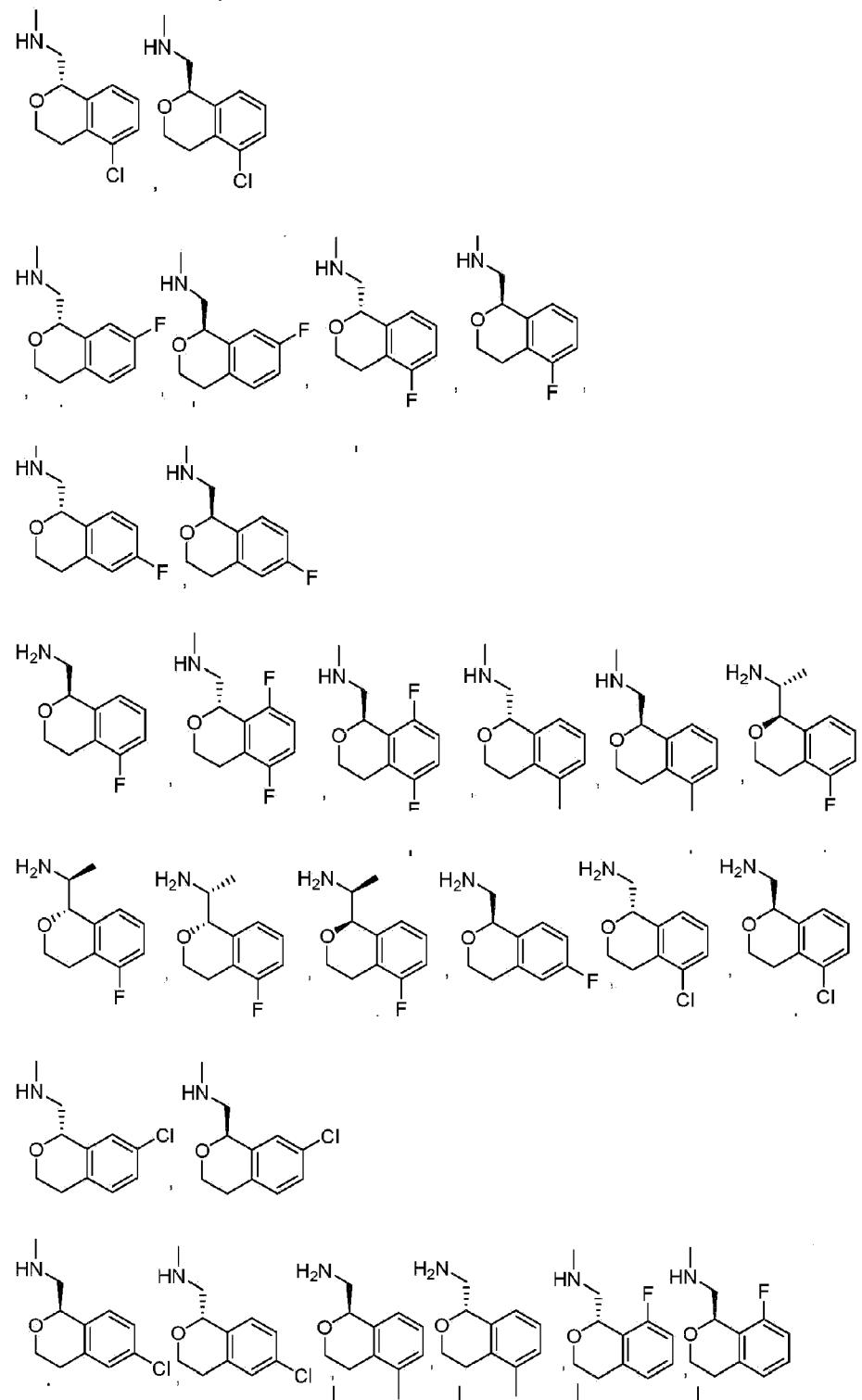


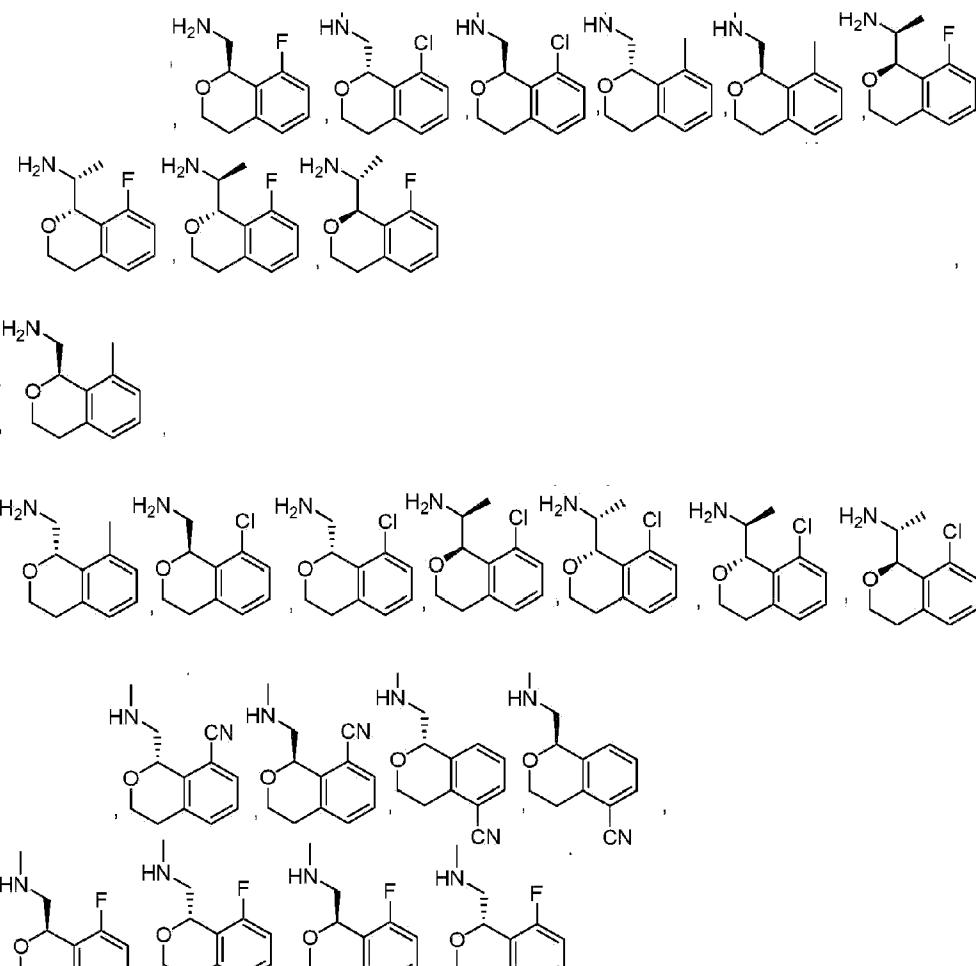
[0027] In other embodiments, C(1) of the isochroman is of absolute configuration:



**[0028]** In one embodiment, provided are compounds of formula (I) which are greater than 90% enantiomerically pure. In another embodiment, provided are compounds of formula I which are greater than 95% enantiomerically pure.

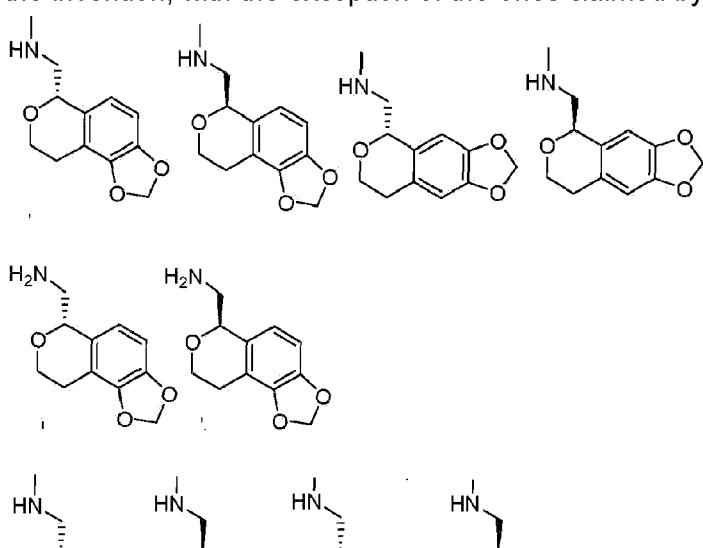
**[0029]** In one embodiment of the invention, provided is a compound according to formula (I), wherein said compound is:

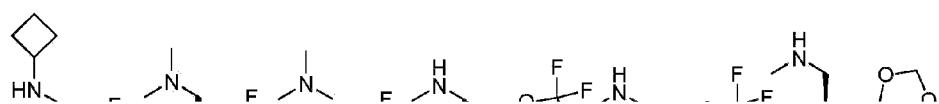
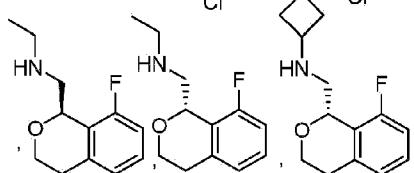
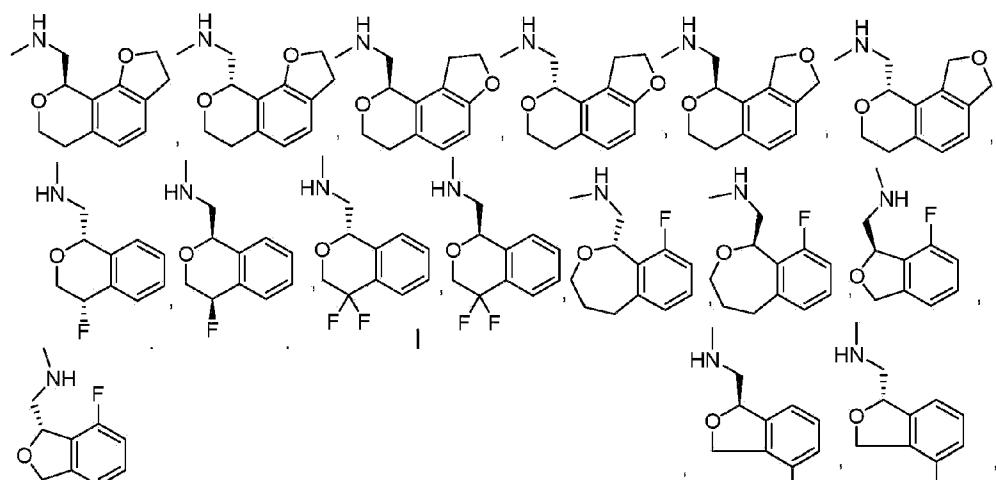
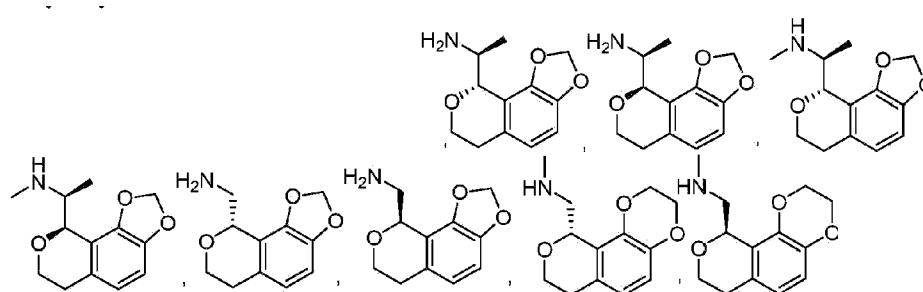
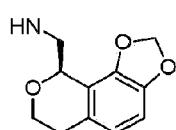
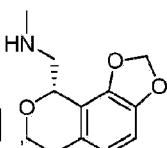
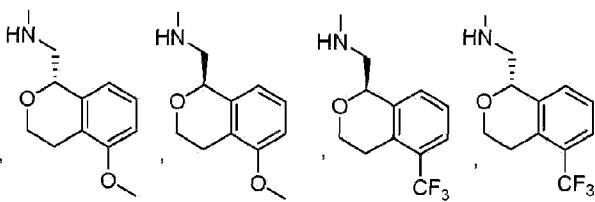
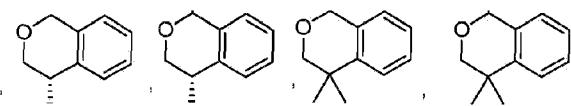


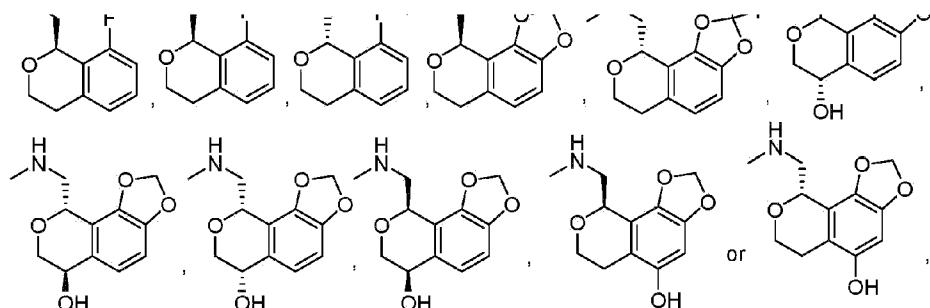


or a pharmaceutically acceptable salt thereof.

The following compounds are also provided for reference, but do not fall under the scope of the invention, with the exception of the ones claimed by the appended claim 25.

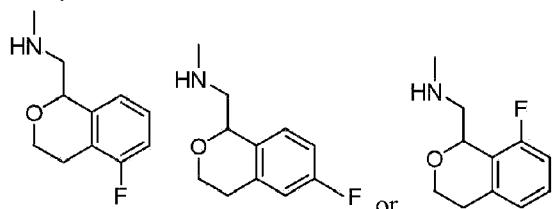






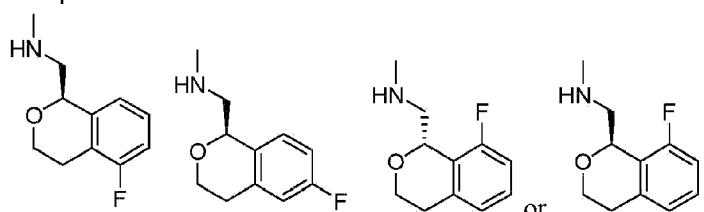
or a pharmaceutically acceptable salt thereof.

**[0030]** In one embodiment, provided is a compound according to formula I, wherein said compound is:



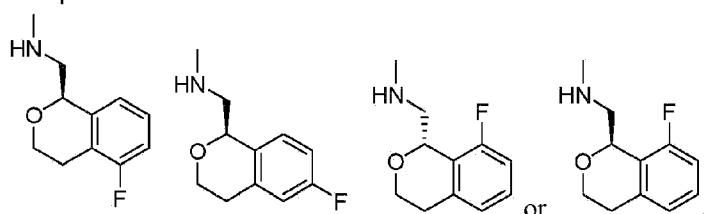
or a pharmaceutically acceptable salt thereof.

**[0031]** In another embodiment, provided is a compound according to formula (I), wherein said compound is:



or a pharmaceutically acceptable salt thereof.

**[0032]** In another embodiment, provided is a compound according to formula (I), wherein said compound is:



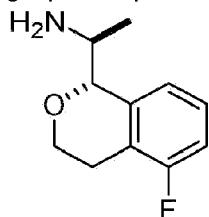
and has greater than 90% enantiomeric purity. In another embodiment, said compound has greater than 95% enantiomeric purity.

**Compounds and Compositions and Definitions:**

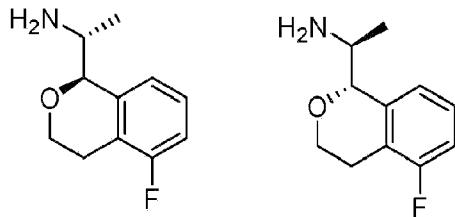
**[0033]** Compounds and compositions of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. A comprehensive

list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of Organic Chemistry. The definitions therein, which are typically presented in a table entitled "Standard List of Abbreviations" are the definitions used herein.

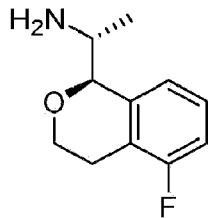
**[0034]** The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are a modified version of the denotations taken from Maehr J. Chem. Ed. 62, 114-120 (1985): simple lines provide no information about stereochemistry and convey only connectivity; solid and broken wedges are used to denote the absolute configuration of a chiral element; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but not necessarily denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of the indicated relative stereochemistry of indeterminate absolute configuration. For example, the graphic representation:



indicates a *trans* relationship between the two chiral centers, that is, either or both of the two representations below:



in any ratio, from pure enantiomers to racemates, while the representation:



indicates a single enantiomer with the absolute configuration depicted, e.g., *((R)-1-((R)-5-fluoroisochroman-1-yl)ethan-1-amine* in the illustration above. In the text describing the stereochemistry of the examples, the convention of Chemical Abstracts is used. Thus "*(R)-1-((R)-5-rel-...*" indicates that the two chiral centers are in that relative relationship, which would be depicted in a structural diagram by solid bold and dashed lines, whereas "*(R)-1-((R)-5-...*" without the "rel" indicates a single enantiomer of that absolute configuration, which would be depicted in a structural diagram by solid and broken wedges.

**[0035]** The "enantiomeric excess" or "% enantiomeric excess" of a composition can be calculated using the equation shown below. In the example shown below, a composition contains 90% of one enantiomer, e.g., the S enantiomer, and 10% of the other enantiomer, e.g., the R enantiomer.  $ee = (90-10)/100 = 80\%$ .

**[0036]** Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. Some compositions described herein contain an enantiomeric excess of at least about 50%, 75%, 90%, 95%, or 99% of the S enantiomer. In other words, the compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. In other embodiments, some compositions described herein contain an enantiomeric excess of at least about 50%, 75%, 90%, 95%, or 99% of the R enantiomer. In other words, the compositions contain an enantiomeric excess of the R enantiomer over the S enantiomer.

**[0037]** For instance, an isomer/enantiomer can, in some embodiments, be provided substantially free of the corresponding enantiomer, and can also be referred to as "optically enriched," "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used interchangeably herein. These terms refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1: 1 by weight). For example, an enantiomerically enriched preparation of the S enantiomer, means a preparation of the compound having greater than about 50% by weight of the S enantiomer relative to the R enantiomer, such as at least about 75% by weight, further such as at least about 80% by weight. In some embodiments, the enrichment can be much greater than about 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least about 85% by weight of one enantiomer relative to other enantiomer, such as at least about 90% by weight, and further such as at least 95% by weight. In certain embodiments, the compound provided herein is made up of at least about 90% by weight of one enantiomer. In other embodiments, the compound is made up of at least about 95%, 98%, or 99% by weight of one enantiomer.

**[0038]** In some embodiments, the compound is a racemic mixture of (S)- and (R)-isomers. In other embodiments, provided herein is a mixture of compounds wherein individual compounds of the mixture exist predominately in an (S)- or (R)-isomeric configuration. For example, the compound mixture has an (S)-enantiomeric excess of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more. In other embodiments, the compound mixture has an (S)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

**[0039]** In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about

90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5% or more. In some other embodiments, the compound mixture has an (R)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5% or more.

**[0040]** In other embodiments, the compound mixture contains identical chemical entities except for their stereochemical orientations, namely (S)- or (R)-isomers. For example, if a compound disclosed herein has --CH(R)-- unit, and R is not hydrogen, then the --CH(R)-- is in an (S)- or (R)-stereochemical orientation for each of the identical chemical entities. In some embodiments, the mixture of identical chemical entities is a racemic mixture of (S)- and (R)-isomers. In another embodiment, the mixture of the identical chemical entities (except for their stereochemical orientations), contain predominately (S)-isomers or predominately (R)-isomers. For example, the (S)-isomers in the mixture of identical chemical entities are present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more, relative to the (R)-isomers. In some embodiments, the (S)-isomers in the mixture of identical chemical entities are present at an (S)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5% or more.

**[0041]** In another embodiment, the (R)-isomers in the mixture of identical chemical entities (except for their stereochemical orientations), are present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more, relative to the (S)-isomers. In some embodiments, the (R)-isomers in the mixture of identical chemical entities (except for their stereochemical orientations), are present at a (R)-enantiomeric excess greater than about 55% to about 99.5%, greater than about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

**[0042]** Hydrocarbyl refers to any substituent comprised of hydrogen and carbon as the only elemental constituents. C<sub>1</sub> to C<sub>20</sub> hydrocarbon includes, for example, alkyl, cycloalkyl, polycycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include benzyl,

phenethyl, cyclohexylmethyl, adamantyl, camphoryl and naphthylethyl. Aromatic hydrocarbons include benzene (phenyl), naphthalene (naphthyl), anthracene, etc. Aliphatic hydrocarbons are hydrocarbons that are not aromatic; they may be saturated or unsaturated, cyclic, linear or branched, or combinations thereof. Aliphatic hydrocarbons include, for example, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, and combinations thereof. Non-limiting examples of aliphatic hydrocarbons include isopropyl, 2-butenyl, 2-butynyl, cyclopentyl, cyclopropylmethyl, norbornyl, and the like.

**[0043]** Unless otherwise specified, alkyl (or alkylene) is intended to include linear or branched saturated hydrocarbon structures and combinations thereof. Alkyl refers to alkyl groups from 1 to 20 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like.

**[0044]** Cycloalkyl is a subset of hydrocarbon and includes cyclic hydrocarbon groups of from 3 to 8 carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, norbornyl and the like.

**[0045]** Unless otherwise specified, the term "carbocycle" is intended to include ring systems in which the ring atoms are all carbon but of any oxidation state. Thus (C<sub>3</sub>-C<sub>10</sub>) carbocycle refers to both non-aromatic and aromatic systems, including such systems as cyclopropane, benzene and cyclohexene; (C<sub>8</sub>-C<sub>12</sub>) carbopolycycle refers to such systems as norbornane, decalin, indane and naphthalene. Carbocycle, if not otherwise limited, refers to monocycles, bicycles and polycycles, including bridged structures.

**[0046]** Heterocycle means an aliphatic or aromatic carbocycle residue in which from one to four carbons is replaced by a heteroatom selected from the group consisting of N, O, and S. The nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. Unless otherwise specified, a heterocycle may be non-aromatic (heteroaliphatic) or aromatic (heteroaryl). Heterocycle, if not otherwise limited, refers to monocycles, bicycles and polycycles, including bridged structures. Examples of heterocycles include, but are not limited to, pyrrolidine, pyrazole, pyrrole, indole, quinoline, isoquinoline, tetrahydroisoquinoline, benzofuran, benzodioxan, benzodioxole (commonly referred to as methylenedioxyphenyl, when occurring as a substituent), tetrazole, morpholine, thiazole, pyridine, pyridazine, pyrimidine, thiophene, furan, oxazole, oxazoline, isoxazole, atropine, dioxane, tetrahydrofuran and the like. Examples of heterocycl residues include piperazinyl, piperidinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, tetrahydrofuryl, tetrahydropyran, thienyl (also historically called thiophenyl), benzothienyl, thiamorpholinyl, oxadiazolyl, triazolyl, dihydrofuryl, dioxole, dihydropyran and tetrahydroquinolinyl.

**[0047]** Hydrocarbyloxy refers to groups of from 1 to 20 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms attached to the parent structure through

an oxygen. Alkoxy is a subset of hydrocarbyloxy and includes groups of a straight or branched configuration. Examples include methoxy, ethoxy, propoxy, isopropoxy and the like. Lower-alkoxy refers to groups containing one to four carbons. The term "halogen" means fluorine, chlorine, bromine or iodine atoms.

**[0048]** The term "halogen" means fluorine, chlorine, bromine or iodine. In one embodiment, halogen may be fluorine or chlorine. In a further embodiment, the halogen is fluorine.

**[0049]** Unless otherwise specified, acyl refers to formyl and to groups of 1, 2, 3, 4, 5, 6, 7 and 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. Examples include acetyl, benzoyl, propionyl, isobutyryl and the like. Lower-acyl refers to groups containing one to four carbons. The double bonded oxygen, when referred to as a substituent itself is called "oxo".

**[0050]** As used herein, the term "optionally substituted" may be used interchangeably with "unsubstituted or substituted". The term "substituted" refers to the replacement of one or more hydrogen atoms in a specified group with a specified radical. For example, substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein one or more H atoms in each residue are replaced with halogen, haloalkyl, hydrocarbyl, acyl, alkoxyalkyl, hydroxy lower alkyl, carbonyl, phenyl, heteroaryl, benzenesulfonyl, hydroxy, hydrocarbyloxy, haloalkoxy, oxaalkyl, carboxy, alkoxy carbonyl [-C(=O)O-alkyl], alkoxy carbonyl amino [HNC(=O)O-alkyl], aminocarbonyl (also known as carboxamido) [-C(=O)NH<sub>2</sub>], alkylaminocarbonyl [-C(=O)NH-alkyl], dialkylaminocarbonyl [-C(=O)N(alkyl)<sub>2</sub>], cyano, acetoxy, nitro, amino, alkylamino, dialkylamino, (alkyl)(aryl)aminoalkyl, alkylaminoalkyl (including cycloalkylaminoalkyl), dialkylaminoalkyl, dialkylaminoalkoxy, heterocyclylalkoxy, mercapto, alkylthio, sulfoxide, sulfone, sulfonyl amino, alkylsulfinyl, alkylsulfonyl, acylaminoalkyl, acylaminoalkoxy, acylamino, amidino, aryl, benzyl, heterocyclyl, heterocyclylalkyl, phenoxy, benzyloxy, heteroaryloxy, hydroxyimino, alkoxyimino, oxaalkyl, aminosulfonyl, trityl, amidino, guanidino, ureido, benzyloxyphenyl, and benzyloxy. "Oxo" is also included among the substituents referred to in "optionally substituted"; it will be appreciated by persons of skill in the art that, because oxo is a divalent radical, there are circumstances in which it will not be appropriate as a substituent (e.g. on phenyl). In one embodiment, 1, 2, or 3 hydrogen atoms are replaced with a specified radical. In the case of alkyl and cycloalkyl, more than three hydrogen atoms can be replaced by fluorine; indeed, all available hydrogen atoms could be replaced by fluorine. In particular embodiments, substituents are halogen, halo(C<sub>1</sub>-C<sub>4</sub>)hydrocarbyl, halo(C<sub>1</sub>-C<sub>4</sub>)hydrocarbyloxy, cyano, thiocyanato, (C<sub>1</sub>-C<sub>4</sub>)hydrocarbylsulfinyl, (C<sub>1</sub>-C<sub>4</sub>)hydrocarbyl-sulfonyl, aminosulfonyl, nitro, acetyl, and acetamido. Preferred substituents are halogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)fluoroalkyl, (C<sub>1</sub>-C<sub>4</sub>)fluoroalkoxy, hydroxy, amino, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, (C<sub>1</sub>-C<sub>4</sub>)acylamino, (C<sub>1</sub>-C<sub>4</sub>)fluoroalkyl and (C<sub>1</sub>-C<sub>4</sub>)fluoroalkoxy.

**[0051]** Substituents R<sup>n</sup> are generally defined when introduced and retain that definition

throughout the specification and claims.

**[0052]** As used herein, and as would be understood by the person of skill in the art, the recitation of "a compound" - unless expressly further limited - is intended to include salts of that compound. Thus, for example, the recitation "a compound of formula I" as depicted above, which contains a basic amine residue  $-NR^3R^4$ , would include salts  $-NHR^3R^4 + X^-$  wherein  $X^-$  is any counterion. In a particular embodiment, the term "compound of formula I" refers to the compound or a pharmaceutically acceptable salt thereof; this term refers to a pharmaceutically acceptable salt of the compound, even if not explicitly stated. Unless otherwise stated or depicted, structures depicted herein are also meant to include all stereoisomeric (e.g., enantiomeric, diastereomeric, and cis-trans isomeric) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and cis-trans isomeric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a  $^{13}C$ - or  $^{14}C$ -enriched carbon are within the scope of this invention. In addition to therapeutic uses, such compounds are useful, for example, as analytical tools or probes in biological assays.

**[0053]** As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginic acid, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Although pharmaceutically acceptable counter ions will be preferred for preparing pharmaceutical

formulations, other anions are quite acceptable as synthetic intermediates. Thus X may be pharmaceutically undesirable anions, such as iodide, oxalate, trifluoromethanesulfonate and the like, when such salts are chemical intermediates.

**[0054]** Unless otherwise specified, the word "includes" (or any variation thereon, e.g., "include", "including", etc.) is intended to be open-ended. For example, "A includes 1, 2 and 3" means that A includes but is not limited to 1, 2 and 3.

**[0055]** Unless otherwise specified, the phrase "such as" is intended to be open-ended. For example, "A can be a halogen, such as chlorine or bromine" means that A can be, but is not limited to, chlorine or bromine.

**[0056]** According to another embodiment, the invention provides a composition comprising a compound of this invention (or its pharmaceutically acceptable salt) and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In some embodiments, the amount of compound in compositions of this invention is such that is effective to treat, prevent, and/or manage various neurological and/or psychiatric diseases, disorders and/or symptoms in a subject. In some embodiments, a composition of this invention is formulated for administration to a subject in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a subject.

**[0057]** As used herein, the term "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys.

**[0058]** In certain embodiments, provided herein is a composition (e.g., a pharmaceutical composition) comprising a compound described herein and a pharmaceutically acceptable excipient or carrier. In some embodiments, provided herein is a method of treating neurological or psychiatric diseases and disorders in a subject in need thereof in a subject, comprising administering an effective amount of a compound or a pharmaceutical composition described herein. Examples of carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. *Remington: The Science and Practice of Pharmacy*. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. *Handbook of Pharmaceutical Excipients*. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or

pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

**[0059]** Compositions of the present invention may be administered orally, parenterally, by inhalation, topically, rectally, nasally, buccally, sublingually, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the 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 non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including capsules, tablets, aqueous suspensions or solutions.

**[0060]** The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon a variety of factors, including the host treated and the particular mode of administration. It should also be understood that a specific dosage and treatment regimen for any particular subject will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

**[0061]** As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

**[0062]** In some embodiments, the invention provides a compound of the invention (or a pharmaceutically acceptable salt thereof) or a composition comprising a compound of this invention (or its pharmaceutically acceptable salt), for use in a method for treating a neurological or psychiatric disease or disorder in a subject, the method comprising administering to the subject an effective amount of the compound (or its pharmaceutically acceptable salt), or composition. Neurological and/or psychiatric diseases and disorders can

exhibit a variety of psychiatric and behavioral symptoms, including apathy, depression, anxiety, cognitive impairment, psychosis, aggression, agitation, poor impulse control and sleep disruptions.

**[0063]** In one embodiment, the neurological or psychiatric disease or disorder is bipolar disorder, anxiety, depression, Alzheimer's Disease with agitation, Alzheimer's Disease with aggression or Alzheimer's Disease with agitation aggression.

**[0064]** In one embodiment, the neurological or psychiatric disease or disorder is bipolar disorder, anxiety, depression, dementia, Alzheimer's Disease, Alzheimer's Disease with agitation, Alzheimer's Disease with aggression or Alzheimer's Disease with agitation aggression, a neurocognitive disorder, a neurocognitive disorder with behavioral and psychological symptoms.

**[0065]** In one embodiment, the neurological or psychiatric disease or disorder are behavioral and psychological symptoms of a neurocognitive disorder including dementia and Alzheimer's disease. The behavioral and psychological symptoms include disturbances in perception, thought content, mood, or behaviors including delusions (distressing beliefs), hallucinations, agitation (easily upset, repeating questions, arguing or complaining, hoarding, pacing, inappropriate screaming, crying out, disruptive sounds, rejection of care leaving home), aggression (physical or verbal), depression or dysphoria, anxiety (worrying, shadowing), apathy or indifference, disinhibition (socially inappropriate behavior, sexually inappropriate behavior, irritability or lability, motor disturbance (repetitive activities without purpose, wandering, rummaging, night-time behaviors (waking and getting up at night) impulsivity, attentional deficits, executive dysfunction.

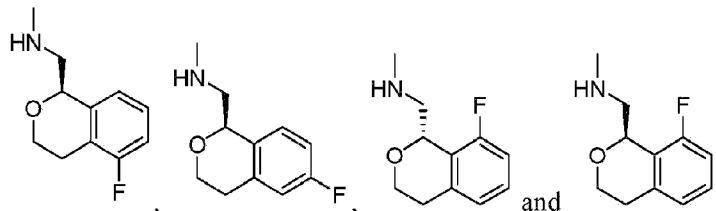
**[0066]** Assays were used herein to identify representative candidate treatments. Examples of candidate treatments include, without limitation, treatment of Alzheimer's Disease with agitation, Alzheimer's Disease with aggression and Alzheimer's Disease with agitation aggression. Aggression and agitation are common symptoms in neurological and psychiatric diseases and disorders. Aggression and agitation have been associated with hyperactivity in subcortical brain regions, which can be modelled in animals using psychostimulants (eg PCP, Amphetamine). For example, psychostimulants induce hyperlocomotor activity (HLA) in animals. Antipsychotics (eg. haloperidol, clozapine and risperidone) have been shown to reduce psychostimulant-induced HLA and are efficacious against agitation in Alzheimer's disease. Other drugs used off-label, or are currently under study in clinical trials, for agitation in Alzheimer's disease are mood stabilizers, such as lithium (which also decreases Amphetamine-induced HLA), and antidepressants (eg. citalopram). Antidepressants demonstrate activity in assays such as the forced swim and tail suspension tests. Therefore, the aforementioned assays were helpful in identifying candidate treatments for agitation in Alzheimer's disease and agitation/aggression in other neurological and psychiatric diseases and disorders.

**[0067]** In one embodiment, a compound according to formula I or a pharmaceutically

acceptable salt thereof is provided, for use in a method of treating a bipolar disorder in a subject in need thereof, the method comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

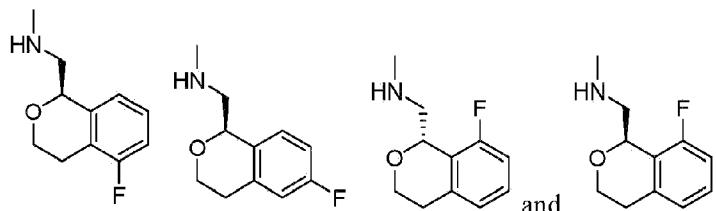
**[0068]** In one embodiment, a compound according to formula I or a pharmaceutically acceptable salt thereof is provided, for use in a method of treating anxiety in a subject in need thereof, the comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

**[0069]** In one embodiment, provided is a compound selected from:



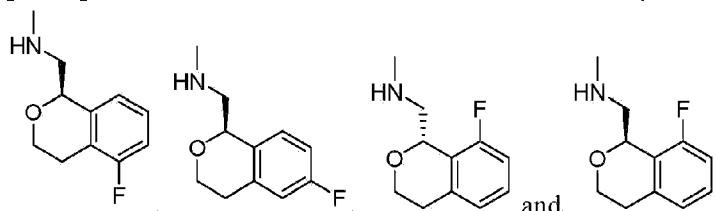
or a pharmaceutically acceptable salt thereof, for use in a method of treating a neurological or psychiatric disease or disorder selected from bipolar disorder, anxiety, depression, Alzheimer's Disease with agitation, Alzheimer's Disease with aggression or Alzheimer's Disease with agitation aggression in a subject in need thereof, the method comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

**[0070]** In one embodiment, a compound selected from:



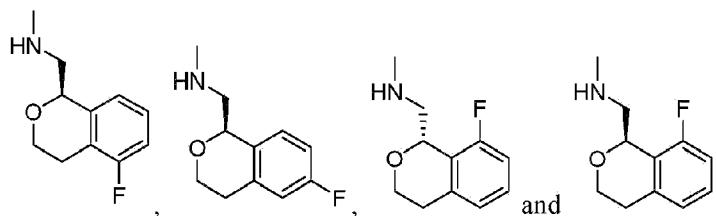
or a pharmaceutically acceptable salt thereof, is provided for use in a method of treating bipolar disorder in a subject in need thereof, the method comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

**[0071]** In one embodiment of the invention, a compound selected from



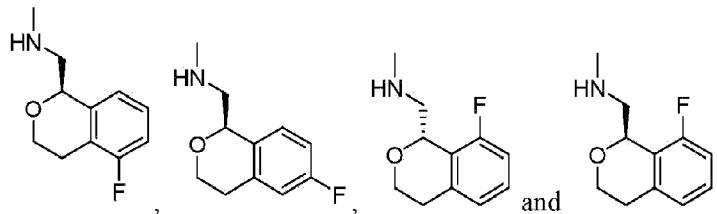
or a pharmaceutically acceptable salt thereof, is provided for use in a method of treating anxiety in a subject in need thereof, the method comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

**[0072]** In one embodiment of the invention, a compound selected from



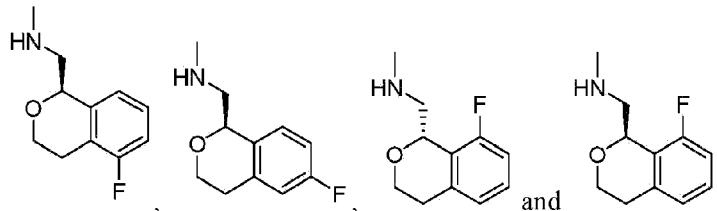
or a pharmaceutically acceptable salt thereof, is provided for use in a method of treating depression in a subject in need thereof, the method comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

**[0073]** In one embodiment of the invention, a compound selected from:



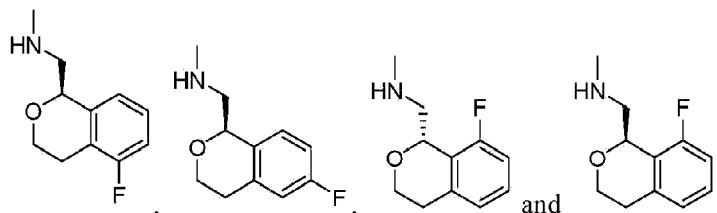
or a pharmaceutically acceptable salt thereof, is provided for use in a method of treating Alzheimer's Disease with agitation in a subject in need thereof, the method comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

**[0074]** In one embodiment of the invention, a compound selected from:



or a pharmaceutically acceptable salt thereof, is provided for use in a method of treating Alzheimer's Disease with aggression in a subject in need thereof, the method comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

**[0075]** In one embodiment of the invention, a compound selected from:



or a pharmaceutically acceptable salt thereof, is provided for use in a method of treating Alzheimer's Disease with agitation aggression in a subject in need thereof, the method comprising the step of administering to said subject an effective amount of the compound or pharmaceutically acceptable salt thereof.

**[0076]** In some embodiments, the neurological or psychiatric disease or disorder is selected from a psychosis, including schizophrenia (paranoid, disorganized, catatonic or

undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced or drug-induced (e.g., phencyclidine, ketamine and other dissociative anesthetics, amphetamine and other psychostimulants and cocaine) psychosis; psychotic disorder, psychosis associated with affective disorders, brief reactive psychosis, schizoaffective psychosis, "schizophrenia-spectrum" disorders such as schizoid or schizotypal personality disorders, or illness associated with psychosis (such as major depression, manic depressive (bipolar) disorder, Alzheimer's disease and post-traumatic stress syndrome), including both positive, negative, and cognitive symptoms of schizophrenia and other psychoses; cognitive disorders including dementia (semantic dementia, frontotemporal dementia, dementia with depressive features, persisting, subcortical dementia, dementia with Lewy Bodies, Parkinsonism-ALS Dementia Complex, and dementia associated with Alzheimer's disease, ischemia, multi-infarct dementia, trauma, vascular problems, stroke, HIV disease, Parkinson's disease, Huntington's disease, Down syndrome, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, or substance abuse), delirium, amnestic disorders or age related cognitive decline; anxiety disorders including acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; substance-related disorders and addictive behaviors (including substance-induced delirium, persisting dementia, persisting amnestic disorder, psychotic disorder or anxiety disorder; tolerance, dependence or withdrawal from substances including alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); eating disorders such as obesity, bulimia nervosa, pica and compulsive eating disorders; bipolar disorders, including bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorders, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorders, depressive disorders including unipolar depression, seasonal depression and post-partum depression, atypical depression, catatonic depression, elderly depression, endogenous depression, melancholic depression, perinatal depression, situational depression, chronic depression, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PDD), mood disorders due to a general medical condition, and substance-induced mood disorders; attention, learning and development disorders such as pervasive developmental disorder including autistic disorder, attention disorders including attention-deficit hyperactivity disorder (ADHD) and conduct disorder, disorders such as autism and autism spectrum disorders (including Asperger's syndrome, pervasive developmental disorder, Rett Syndrome and Fragile X Syndrome), depression, benign forgetfulness, childhood learning disorders, specific learning disorders, intellectual development disorders, and closed head injury; movement disorders and symptoms, including tremors, dyskinesia, dystonia, tics, dysphonia, ataxia, myoclonus, Essential Tremor, Tardive Dyskinesia, Restless Leg Syndrome, Tourette Syndrome, Multiple System Atrophy, Multiple Sclerosis, Huntington's Disease, Parkinson's Disease and Atypical Parkinsonisms; epilepsy; urinary incontinence; neuronal damage including ocular damage, retinopathy or macular degeneration of the eye, tinnitus, hearing impairment and loss, and brain edema; emesis; and sleep disorders including

insomnia, disturbed sleep, jet lag, hypersomnia, cataplexy, sleep apnea, obstructive sleep apnia, REM sleep behavior disorder, Restless Leg Syndrome, periodic limb movement disorder, circadian rhythm sleep disorders, delayed sleep phase disorder, sleepwalking, night terrors, bed wetting, rapid eye movement sleep behavior disorder, shift work sleep disorder, excessive daytime sleepiness, non-24-hour sleep-wake disorder, sleep paralysis and narcolepsy.

**[0077]** In some embodiments, the neurological or psychiatric disease or disorder is Alzheimer's disease, Parkinson's disease, depression, cognitive impairment, stroke, schizophrenia, Down syndrome, or Fetal Alcohol Syndrome. In some embodiments, the neurological or psychiatric disorder is Alzheimer's disease. In some embodiments, the neurological or psychiatric disorder is Parkinson's disease. In some embodiments, the neurological or psychiatric disorder is depression. In some embodiments, the neurological or psychiatric disorder is cognitive impairment. In some embodiments, the cognitive impairment is cognitive dysfunction associated with depression, for example, major depressive disorder. In some embodiments, the neurological or psychiatric disorder is stroke. In some embodiments, the neurological or psychiatric disorder is schizophrenia. In some embodiments, the neurological or psychiatric disorder is Down syndrome. In some embodiments, the neurological or psychiatric disorder is Fetal Alcohol Syndrome.

**[0078]** In some embodiments, the neurological or psychiatric disease or disorder is bipolar disorder. Bipolar disorders (including both bipolar I and bipolar II) are serious psychiatric disorders that have a prevalence of approximately 2% of the population, and affects both genders alike. It is a relapsing-remitting condition characterized by cycling between elevated (i.e., manic) and depressed moods, which distinguishes it from other disorders such as major depressive disorder and schizophrenia. Bipolar I is defined by the occurrence of a full manic episode, although most individuals experience significant depression. Symptoms of mania include elevated or irritable mood, hyperactivity, grandiosity, decreased need for sleep, racing thoughts and in some cases, psychosis. The depressive episodes are characterized by anhedonia, sad mood, hopelessness, poor self-esteem, diminished concentration and lethargy. Bipolar II is defined as the occurrence of a major depressive episode and hypomanic (less severe mania) episode although subjects spend considerable more time in the depressive state. Other related conditions include cyclothymic disorder.

**[0079]** In some embodiments, the neurological or psychiatric disease or disorder is schizophrenia. Schizophrenia is a disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by characteristics such as psychotic symptoms, phasic progression and development, and/or deterioration in social behavior and professional capability. Characteristic psychotic symptoms are disorders of thought content (e.g., multiple, fragmentary, incoherent, implausible or simply delusional contents, or ideas of persecution) and of mentality (e.g., loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (e.g., hallucinations), emotions (e.g., superficial or inadequate emotions), self-perceptions, intentions, impulses, and/or inter-human relationships, and psychomotoric disorders (e.g., catatonia). Other symptoms are also

associated with this disorder. Schizophrenia is classified into subgroups: the paranoid type, characterized by delusions and hallucinations and absence of thought disorder, disorganized behavior, and affective flattening; the disorganized type, also named "hebephrenic schizophrenia," in which thought disorder and flat affect are present together; the catatonic type, in which prominent psychomotor disturbances are evident, and symptoms may include catatonic stupor and waxy flexibility; and the undifferentiated type, in which psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met. The symptoms of schizophrenia normally manifest themselves in three broad categories: positive, negative and cognitive symptoms. Positive symptoms are those which represent an "excess" of normal experiences, such as hallucinations and delusions. Negative symptoms are those where the subject suffers from a lack of normal experiences, such as anhedonia and lack of social interaction. The cognitive symptoms relate to cognitive impairment in schizophrenics, such as lack of sustained attention and deficits in decision making.

**[0080]** In some embodiments, the neurological or psychiatric disease or disorder is anxiety disorder. Anxiety disorders are characterized by fear, worry, and uneasiness, usually generalized and unfocused as an overreaction to a situation. Anxiety disorders differ in the situations or types of objects that induce fear, anxiety, or avoidance behavior, and the associated cognitive ideation. Anxiety differs from fear in that anxiety is an emotional response to a perceived future threat while fear is associated with a perceived or real immediate threat. They also differ in the content of the associated thoughts or beliefs. Examples of anxiety disorders include separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder (social phobia), panic disorder, panic attack specifier, agoraphobia, generalized anxiety disorder, substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, illness anxiety disorder, social (pragmatic) communication disorder, other specified anxiety disorder, and unspecified anxiety disorder; stressor-related disorders, including reactive attachment disorder, disinhibited social engagement disorder, posttraumatic stress disorder (PTSD), acute stress disorder, and adjustment disorders.

**[0081]** Cognitive impairment includes a decline in cognitive functions or cognitive domains, e.g., working memory, attention and vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving (e.g., executive function, speed of processing and/or social cognition). In particular, cognitive impairment may indicate deficits in attention, disorganized thinking, slow thinking, difficulty in understanding, poor concentration, impairment of problem solving, poor memory, difficulties in expressing thoughts, and/or difficulties in integrating thoughts, feelings and behavior, or difficulties in extinction of irrelevant thoughts.

**[0082]** In some embodiments, the neurological or psychiatric disease or disorder involves a deficit in cognition (cognitive domains as defined by the DSM-5 are: complex attention, executive function, learning and memory, language, perceptual-motor, social cognition). In some embodiments, the neurological or psychiatric disorder is associated with a deficit in dopamine signaling. In some embodiments, the neurological or psychiatric disorder is associated with basal ganglia dysfunction. In some embodiments, the neurological or

psychiatric disorder is associated with dysregulated locomotor activity. In some embodiments, the neurological or psychiatric disorder is associated with impairment of prefrontal cortex functioning.

**[0083]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating one or more symptoms of a neurological and/or psychiatric disease or disorder provided herein. Such diseases or disorders include mood disorders, including bipolar I disorder, bipolar II disorder, mania, cyclothymic disorder, substance/medication-induced bipolar and related disorders, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorders; psychotic disorders, including schizophrenia, schizophrenia spectrum disorder, acute schizophrenia, chronic schizophrenia, NOS schizophrenia, schizoid personality disorder, schizotypal personality disorder, delusional disorder, psychosis, psychotic disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, drug-induced psychosis (e.g., cocaine, alcohol, amphetamine), schizoaffective disorder, agitation, aggression, delirium, catatonia, dissociative identity disorder, paranoid personality disorder, psychotic depression, Schizotypal Personality Disorder, Childhood Disintegrative Disorder (Heller's Syndrome), Disintegrative Psychosis, Dissociative Amnesia, Somatic Symptom Disorder, Parkinson's psychosis, excitatory psychosis, Tourette's syndrome, and organic or NOS psychosis; depressive disorders, including disruptive mood dysregulation disorder, major depressive disorder (MDD) (including major depressive episode), dysthymia, persistent depressive disorder (dysthymia), treatment resistant depression, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder; anxiety disorders; and other disorders including substance abuse or dependency (e.g., nicotine, alcohol, cocaine), addiction, internet gaming disorder, eating disorders, behavior disorder, seizure, vertigo, epilepsy, agitation, aggression, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, dyskinesias, Huntington's disease, dementia, premenstrual dysphoria, attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD), hyperkinetic syndrome, autism, autism spectrum disorder, obsessive-compulsive disorder, pain, fibromyalgia, migraine, cognitive impairment, movement disorder, restless leg syndrome (RLS), multiple sclerosis, Primary Progressive Multiple Sclerosis, Parkinson's disease, Huntington's disease, dyskinesias multiple sclerosis, sleep disorder, sleep apnea, narcolepsy, excessive daytime sleepiness, jet lag, drowsy side effect of medications, insomnia, sexual dysfunction, hypertension, emesis, Lesche-Nyhane disease, Wilson's disease, Rett syndrome, and Huntington's chorea. In some embodiments, the neurological and/or psychiatric disorders include agitation and aggression.

**[0084]** In some embodiments, the agitation and aggression are associated with Alzheimer's disease, Parkinson's disease, and/or autism.

**[0085]** In some embodiments, the neurological and/or psychiatric disease or disorders are obsessive-compulsive disorder and related disorders (e.g., body dysmorphic disorder,

hoarding disorder, trichotillomania, excoriation disorder).

**[0086]** In some embodiments, the neurological and/or psychiatric diseases or disorders are disruptive, impulse-control, and conduct disorders including oppositional defiant disorder, intermittent explosive disorder, conduct disorder, antisocial personality disorder, pyromania, kleptomania, other specified disruptive, impulse-control, and conduct disorder, unspecified disruptive, impulse-control, and conduct disorder.

**[0087]** Depressive disorders include major depressive disorder and dysthymia, and are associated with depressed mood (sadness), poor concentration, insomnia, fatigue, appetite disturbances, excessive guilt and thoughts of suicide.

**[0088]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating one or more symptoms including depression (e.g., major depressive disorder or dysthymia); bipolar disorder, seasonal affective disorder; cognitive deficit; sleep related disorder (e.g., sleep apnea, insomnia, narcolepsy, cataplexy) including those sleep disorders which are produced by psychiatric conditions; chronic fatigue syndrome; anxieties (e.g., general anxiety disorder, social anxiety disorder, panic disorder); obsessive compulsive disorder; post-menopausal vasomotor symptoms (e.g., hot flashes, night sweats); neurodegenerative disease (e.g., Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, progressive bulbar (atrophy) palsy, pseudobulbar palsy spinal muscular atrophy diseases (e.g., SMA type I, also called Werdnig-Hoffmann disease, SMA type II, SMA type III, also called Kugelberg-Welander disease, and Kennedy Disease, also called progressive spinobulbar muscular atrophy), Hallervorden-Spatz disease, Seitelberger disease (Infantile Neuroaxonal Dystrophy), adrenoleukodystrophy, Alexander Disease, autosomal dominant cerebellar ataxia (ADCA), pure autonomic failure (Bradbury-Eggleston Syndrome), CADASII, Syndrome, and neuronal ceroids lipofuscinose disorders such as Batten Disease (Spielmeyer-Vogt-Sjögren)); manic disorder; dysthymic disorder; and obesity.

**[0089]** In some embodiments, a depressive disorder is associated with acute suicidality or suicide ideation. The United States Food and Drug Administration has adopted a "black box" label warning indicating that antidepressants may increase the risk of suicidal thinking and behavior in some children, adolescents and young adults (up to age 24) with a depressive disorder such as MDD. In some embodiments, a provided compound does not increase the risk of suicidal thinking and/or behavior in children, adolescents and/or young adults with a depressive disorder, e.g., with MDD. In some embodiments, the present invention provides a method of treating one or more symptoms of a depressive disorder (e.g., MDD) in children, adolescents and/or young adults without increasing the risk of suicidal thinking and/or behavior.

**[0090]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating one or more

symptoms including senile dementia, Early Onset Alzheimer's Disease, Alzheimer's type dementia, cognition, memory loss, amnesia/amnestic syndrome, disturbances of consciousness, coma, lowering of attention, speech disorder, agnosia, aphasia, apraxia, Mild Cognitive Impairment (MCI), benign forgetfulness, mild neurocognitive disorder, major neurocognitive disorder, neurocognitive disorder due to disease (e.g., Huntington's Disease, Parkinson's disease, Prion Disease, Traumatic Brain Injury, HIV or AIDS), Binswanger's Disease (subcortical leukoencephalopathy), and Capgras Syndrome.

**[0091]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating one or more symptoms of pain, e.g., neuropathic pain, sensitization accompanying neuropathic pain, or inflammatory pain. In some embodiments, the pain is neuropathic pain, including post herpetic (or post-shingles) neuralgia, reflex sympathetic dystrophy/causalgia or nerve trauma, phantom limb pain, carpal tunnel syndrome, and peripheral neuropathy (such as diabetic neuropathy or neuropathy arising from chronic alcohol use). In some embodiments, the pain is acute pain, nociceptive pain, arthritis pain, rheumatoid arthritis, osteoarthritis, joint pain, muscoskeletal pain, back pain, dorsalgia, bulging disc, hip pain, visceral pain, headache, tension headache, acute tension headache, chronic tension headache, chronic cluster headache, common migraine, classic migraine, cluster headache, mixed headache, post-traumatic headache, eye strain headache, Short-lasting Unilateral Neuralgiform (SUNCT) headache, SUNCT Syndrome, herpes zoster, acute herpes zoster, shingles, postherpetic neuralgia (shingles), causalgia, central pain, central pain syndrome, chronic back pain, neuralgia, neuropathic pain syndrome, neuropathy, diabetic neuropathy, diabetes-related neuropathy, diabetes-related nerve pain, fibrositis, peripheral neuropathy caused by chemotherapy, peripheral nerve disease, peripheral neuropathy, nerve pain, nerve trauma, sensitization accompanying neuropathic pain, complex regional pain syndrome, compression neuropathy, craniofacial pain, chronic joint pain, chronic knee pain, chronic pain syndrome, cancer pain, trigeminal neuralgia, tic doloreaux, reflex sympathetic causalgia, painful peripheral neuropathy, spinal nerve injury, arachnoiditis, spinal pain, Bernhardt-Roth Syndrome (meralgia parasthetica), carpal tunnel syndrome, cerebrospinal fluid syndrome, Charcot-Marie-tooth disease, hereditary motor and sensory neuropathy, peroneal muscular atrophy, cluster-tic syndrome, coccygeal pain syndromes, compartment syndrome, degenerative disc disease, failed back surgery syndrome, genito-pelvic pain/penetration disorder, gout, inflammatory pain, lumbar radiculopathy, neuroma (painful scar), pain associated with multiple sclerosis, pelvic floor disorders, phantom limb pain, piriformis syndrome, psychogenic pain, radicular pain syndrome, Raeder's syndrome, referred pain, reflex sympathetic dystrophy syndrome, sciatica, sciatica pain, scoliosis, slipped disc, somatic pain, spinal stenosis, stiff-person syndrome/stiff-man syndrome, stump pain, sympathetically maintained pain, tolosa-hunt syndrome, whiplash, or pain associated with Lyme disease.

**[0092]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating one or more symptoms including obesity; migraine or migraine headache; and sexual dysfunction, in men or women, including without limitation sexual dysfunction caused by psychological and/or

physiological factors, erectile dysfunction, premature ejaculation, vaginal dryness, lack of sexual excitement, inability to obtain orgasm, and psycho-sexual dysfunction, including without limitation, inhibited sexual desire, inhibited sexual excitement, inhibited female orgasm, inhibited male orgasm, functional dyspareunia, functional vaginismus, and atypical psychosexual dysfunction.

**[0093]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of suppressing rapid eye movement (REM) during both sleep and daytime equivalent.

**[0094]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of suppressing or eliminating pathological or excessive REM during the night or daytime equivalent.

**[0095]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating one or more symptoms including cataplexy (sudden involuntary transient bouts of muscle weakness or paralysis while awake); nighttime sleep disturbance/sleep fragmentation associated with narcolepsy or other conditions; sleep paralysis associated with narcolepsy or other conditions; hypnagogic and hypnapompic hallucinations associated with narcolepsy or other conditions; and excessive daytime sleepiness associated with narcolepsy, sleep apnea or shift work disorder and other medical conditions such as cancer, chronic fatigue syndrome and fibromyalgia.

**[0096]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating one or more symptoms of movement diseases or disorders, including akinesias, akinetic-rigid syndromes, dyskinesias and dystonias. Examples of akinesias and akinetic-rigid syndromes include Parkinson's disease, drug-induced Parkinsonism, postencephalitic Parkinsonism, secondary Parkinsonism, Parkinson plus syndromes, atypical Parkinsonism, idiopathic Parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, Parkinsonism-ALS dementia complex and basal ganglia calcification, medication-induced Parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor), Gilles de la Tourette's syndrome, epilepsy, muscular spasms and disorders associated with muscular spasticity or weakness including tremors. Examples of dyskinesias include drug (e.g. L-DOPA) induced dyskinesia tremor (such as rest tremor, postural tremor, intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including generalized myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics). Examples of dystonias include generalized dystonia, idiopathic dystonia, drug-induced dystonia, symptomatic dystonia, paroxysmal dystonia, focal dystonia, blepharospasm, oromandibular dystonia, spasmodic dysphonia, spasmodic torticollis, axial dystonia, dystonic writer's cramp

and hemiplegic dystonia. Other examples of movement diseases or disorders include stereotypic movement disorder, persistent (chronic) motor disorder, medication-Induced movement disorder, psychogenic movement disorders, substance/medication-Induced movement disorder, extrapyramidal movement disorders, hyperkinetic movement disorders, hypokinetic movement disorders, alternating hemiplegia, Angelman syndrome, Hallervorden-Spatz Disease, ataxia, dentate cerebellar ataxia, ataxia telangiectasia (Louis-Bar syndrome), Friedreich's Ataxia, hereditary spinal ataxia, hereditary spinal sclerosis, Machado-Joseph Disease, spinocerebellar ataxia, progressive myoclonic ataxia, athetosis, ballismus, blepharospasm (eye twitching), cerebral palsy, tardive dystonia, tardive dyskinesia, idiopathic torsion dystonia, torsion dystonia, focal dystonia, idiopathic familial dystonia, Idiopathic nonfamilial dystonia, cervical dystonia (spasmodic torticollis), primary dystonia, orofacial dystonia, developmental coordination disorder, bulbospinal muscular atrophy (Kennedy's Disease), Shy-Drager Syndrome, and Stiff-Person (Stiff-Man) Syndrome.

**[0097]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating one or more symptoms of epilepsy and/or seizures, including abdominal epilepsy, absence seizure, acquired epilepsy, acquired epileptiform aphasia, Aicardi syndrome, Alpers' disease, Alpers-Huttenlocher syndrome, Angelman syndrome, benign focal epilepsy, benign focal epilepsy of childhood, benign intracranial hypertension, benign rolandic epilepsy (BRE), CDKL5 disorder, childhood absence epilepsy, dentate cerebellar ataxia, Doose syndrome, Dravet syndrome, dyscognitive focal seizure, epilepsy with grand mal seizures, epilepsy with myoclonic-absences, epileptic hemiplegia, febrile seizures, focal seizure, frontal lobe epilepsy, generalized tonic-clonic seizures, genetic epilepsy, Glut1 deficiency syndrome, hypothalamic hamartoma, idiopathic epilepsy, idiopathic generalized epilepsy, idiopathic localization-related epilepsies, idiopathic partial epilepsy, idiopathic seizure, juvenile absence epilepsy, juvenile myoclonic epilepsy, Lafora disease, Lafora progressive myoclonus epilepsy, Landau-Kleffner syndrome, Lassueur-Graham-Little syndrome, Lennox syndrome, Lennox-Gastaut syndrome, medically refractory epilepsy, mesial-temporal lobe sclerosis, myoclonic seizure, neonatal epilepsy, occipital lobe epilepsy, Ohtahara syndrome, Panayiotopoulos syndrome, parietal lobe epilepsy, PCDH19 epilepsy, photosensitive epilepsy, progressive myoclonic epilepsies, Rasmussen's encephalitis, Rasmussen's syndrome, refractory epilepsy, seizure disorder, status epilepticus, Sturge-Weber syndrome, symptomatic generalized epilepsy, symptomatic parital epilepsy, TBCK-related ID syndrome, temporal lobe epilepsy, temporal lobe seizures, tonic-clonic seizure, West syndrome, tremor, cerebellar tremor, cerebellar outflow tremor, intention tremor, essential tremor, benign essential tremor, Parkinsonian tremor, and medication-induced postural tremor.

**[0098]** In some embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in a method of treating a neurological and/or psychiatric disease or disorder described herein, comprising administering a compound of the invention in conjunction with one or more pharmaceutical agents. Suitable pharmaceutical agents that may be used in combination with the compounds of the present invention include anti-Parkinson's drugs, anti-Alzheimer's drugs, anti-depressants, anti-psychotics, anti-

ischemics, CNS depressants, anti-cholinergics, nootropics, epilepsy medication, attention (e.g., ADD/ADHD) medications, sleep-promoting medications, wakefulness-promoting medications, and pain medications. In some embodiments, suitable pharmaceutical agents are anxiolytics.

**[0099]** Suitable anti-Parkinson's drugs include dopamine replacement therapy (e.g. L-DOPA, carbidopa, COMT inhibitors such as entacapone or tolcapone), dopamine agonists (e.g. D1 agonists, D2 agonists, mixed D1/D2 agonists, bromocriptine, pergolide, cabergoline, ropinirole, pramipexole, piribedil, or apomorphine in combination with domperidone), histamine H2 antagonists, monoamine oxidase inhibitors (such as selegiline, rasagiline, safinamide and tranylcypromine), certain atypical antipsychotics such as pimavanserin (a non-dopaminergic atypical antipsychotic and inverse agonist of the serotonin 5-HT<sub>2A</sub> receptor), and amantadine.

**[0100]** In some embodiments, compounds of the invention can be used in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl(benzhexyl)hydrochloride, COMT inhibitors such as entacapone or tolcapone, MAO A/B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist may be in the form of a pharmaceutically acceptable salt, for example, alentemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate. Lisuride and pramipexole are commonly used in a non-salt form.

**[0101]** Suitable anti-Alzheimer's drugs include beta-secretase inhibitors, gamma-secretase inhibitors, cholinesterase inhibitors such as donepezil, galantamine or rivastigmine, HMG-CoA reductase inhibitors, NSAID's including ibuprofen, vitamin E, and anti-amyloid antibodies. In some embodiments, an anti-Alzheimer's drug is memantine.

**[0102]** Suitable anti-depressants and anti-anxiety agents include norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists,  $\alpha$ -adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT1A agonists or antagonists, especially 5-HT1A partial agonists, and corticotropin releasing factor (CRF) antagonists.

**[0103]** Specific suitable anti-depressant and anti-anxiety agents include amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, citalopram, escitalopram, maprotiline, nortriptyline and protriptyline; fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranylcypromine and selegiline; moclobemide; venlafaxine; desvenlafaxine, duloxetine; aprepitant; bupropion, vilazodone, mirtazapine, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam,

chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, reboxetine, vortioxetine, clorazepate, and ketamine and pharmaceutically acceptable salts thereof. In some embodiments, suitable anti-depressant and anti-anxiety agents are tianeptine, or pharmaceutically acceptable salts thereof.

**[0104]** Suitable anti-psychotic and mood stabilizer agents include D2 antagonists, 5HT2A antagonists, atypical antipsychotics, lithium, and anticonvulsants.

**[0105]** Specific suitable anti-psychotic and mood stabilizer agents include chlorpromazine, fluphenazine, haloperidol, amisulpride, perphenazine, thioridazine, trifluoperazine, aripiprazole, asenapine, clozapine, olanzapine, paliperidone, brexpiprazole, paliperidone, cariprazine, pimavanserin, iloperidone, lumateperone, MIN-101, quetiapine, risperidone, ziprasidone, lurasidone, flupentixol, levomepromazine, pericyazine, perphenazine, pimozide, prochlorperazine, zuclopentixol, olanzapine and fluoxetine, lithium, carbamazepine, lamotrigine, valproic acid, iloperidone, thiothixene, gabapentin, tiagabine and pharmaceutically acceptable salts thereof.

**[0106]** Suitable epilepsy medications include levetiracetam, oxcarbazepine, clobazam, retigabine, zonisamide, felbamate, esliccarbazepine acetate, lacosamide, carbamazepine, tiagabine, methsuximide, progabide, valproic acid, lamotrigine, brivaracetam, rufinamide, topiramate and perampanel.

**[0107]** Suitable attention medications include methyl phenidate, atomoxetine, guanfacine, D-amphetamine, lisdexamphetamine, methylamphetamine, and clonidine.

**[0108]** Suitable sleep-promoting medications include ramelteon, triazolam, zopiclone, eszopiclone, zolpidem, temazepam, and trazodone.

**[0109]** Suitable wakefulness-promoting medications include Modafinil, D-Amphetamine, caffeine, and armodafinil.

**[0110]** Suitable pain medications include dextromethorphan, tapentadol, buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, morphine, naloxegol, oxycodone, tramadol, gabapentil, difluprednate, pregabalin, acetyl salicyclic acid, bromfenac, diclofenac, diflunisal, indomethacin, ketorolac, meoxicam, and naproxen.

**[0111]** In some embodiments, compounds and compositions of the invention may be used in combination with other therapies. Suitable therapies include psychotherapy, cognitive behavioral therapy, electroconvulsive therapy, transcranial magnetic stimulation, vagus nerve stimulation, and deep-brain stimulation.

**[0112]** The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition, the particular agent, its mode of administration, and the like. The compounds and compositions of the invention are

preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment.

**[0113]** The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, sublingually, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In some embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

**[0114]** In some embodiments, a combination of two or more therapeutic agents may be administered together with the compounds of the invention. In some embodiments, a combination of three or more therapeutic agents may be administered with the compounds of the invention.

**[0115]** Other examples of agents the compounds and compositions of this invention may also be combined with include: vitamins and nutritional supplements, antiemetics (e.g. 5-HT3 receptor antagonists, dopamine antagonists, NK1 receptor antagonists, histamine receptor antagonists, cannabinoids, benzodiazepines, or anticholinergics), agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex<sup>®</sup> and Rebif<sup>®</sup>, dalfampridine, alemtuzumab), Copaxone<sup>®</sup>, and mitoxantrone; treatments for Huntington's disease such as tetrabenazine; treatments for asthma such as albuterol and Singulair<sup>®</sup>; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins, fibrates, cholesterol absorption inhibitors, bile acid sequestrants, and niacin; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating immunodeficiency disorders such as gamma globulin; and anti-diabetic agents such as biguanides (metformin, phenformin, buformin), thiazolidinediones (rosiglitazone, pioglitazone, troglitazone), sulfonylureas (tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride, gliclazide), meglitinides (repaglinide, nateglinide), alpha-glucosidase inhibitors (miglitol, acarbose), incretin mimetics (exenatide, liraglutide, taspoglutide), gastric inhibitory peptide analogs, DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, linagliptin, alogliptin), amylin

analogs (pramlintide), and insulin and insulin analogs.

**[0116]** In some embodiments, a compound of the present invention, or a pharmaceutically acceptable salt thereof, is administered in combination with an antisense agent, a monoclonal or polyclonal antibody, or an siRNA therapeutic.

**[0117]** Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another, normally within five hours from one another.

**[0118]** As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

**[0119]** The amount of both, an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive can be administered.

**[0120]** In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 - 100 mg/kg body weight/day of the additional therapeutic agent can be administered.

**[0121]** The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

**[0122]** In some embodiments, the present invention provides a medicament comprising at least one compound of formula I, or a pharmaceutically acceptable salt thereof, and a

pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0123] In some embodiments, the present invention provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a neurological and/or psychiatric disease or disorder.

## EXAMPLES

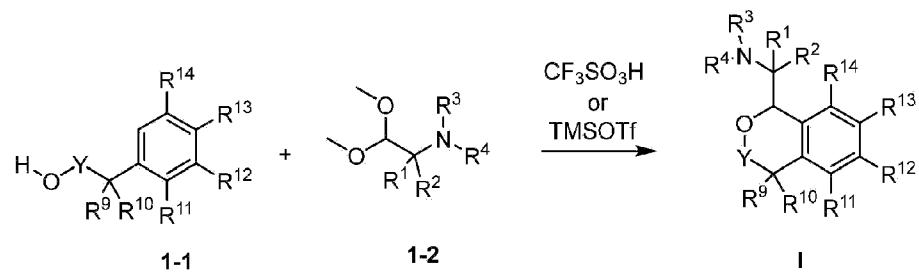
**[0124]** As depicted in the Examples below, in some embodiments, compounds are prepared according to the following procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following methods, and other methods known to persons skilled in the art, can be applied to all compounds and subclasses and species of each of these, as described herein.

## General Schemes

**[0125]** Schemes below provide exemplary synthetic methods for the preparation of the compounds provided herein. One of ordinary skills in the art will understand that similar methods may be employed to prepare the compounds provided herein. In other words, one of ordinary skills in the art will recognize that suitable adjustments to reagents, protecting groups, reaction conditions, reaction sequences, purification methods, and chiral separation conditions may be employed to prepare a desired embodiment. The reactions may be scaled upwards or downwards to suit the amount of material to be prepared.

[0126] In one embodiment, the compound of formula (I) may be prepared following Schemes 1-10 using suitable starting materials known in the art and/or available from a commercial source. In one embodiment, the starting materials of Schemes 1-10 may be prepared from commercially available compounds using procedures and conditions known in the art.

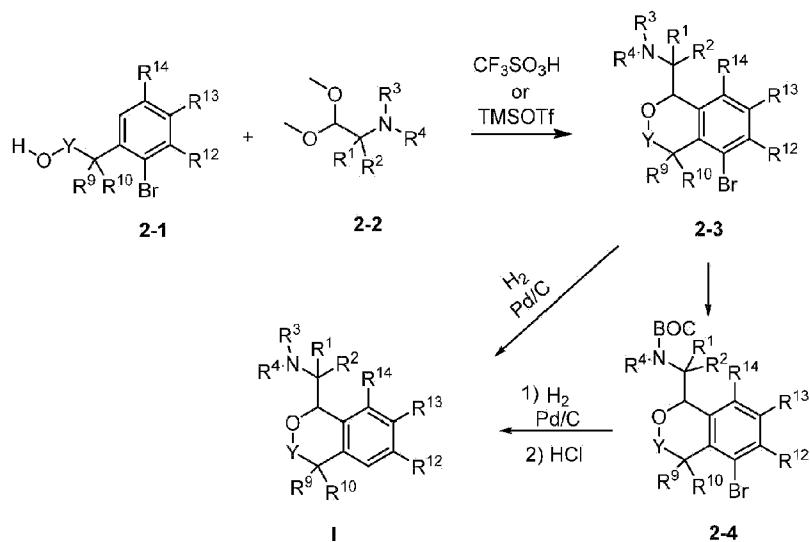
**Scheme 1**



[0127] In one embodiment, a suitable hydroxyalkyl substituted benzene (**1-1**) is reacted with a suitable 2,2-dialkoxy-ethanamine or *N*-protected 2,2-dialkoxy-ethanamine (**1-2**) in the presence of an acid or a Lewis acid such as trifluoromethanesulfonic acid or trimethylsilyl

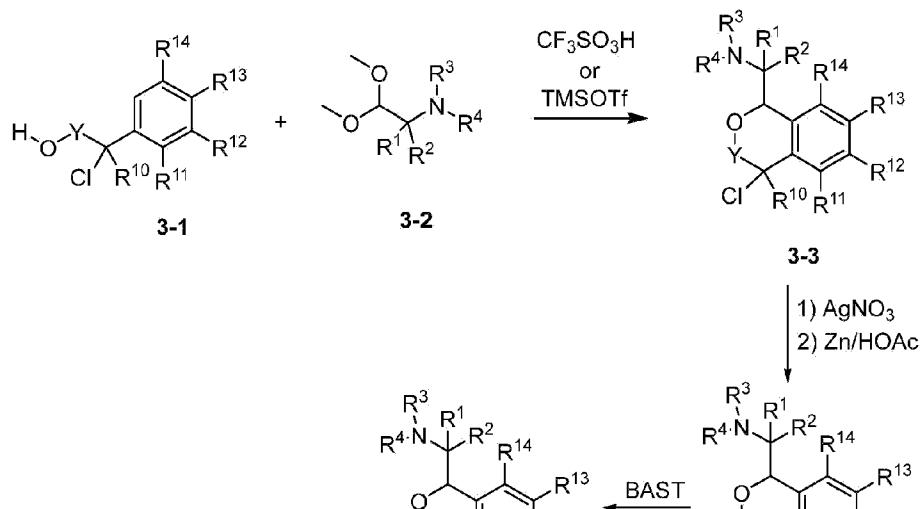
trifluoromethanesulfonate to render the cyclized product (**I**) (Scheme 1), which may be separated using chiral HPLC to provide single enantiomers of formula (**I**). In some cases, to facilitate the purification of **I**, crude **I** was *N*-protected with a BOC-protecting group by reacting **I** with di-*tert*-butyl dicarbonate. After purification, the BOC-group was removed under acidic conditions to afford compound of formula (**I**). The stereoisomers of **I** are separated using HPLC/chiral HPLC to provide single enantiomers (**I**).

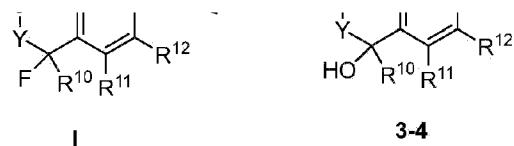
Scheme 2



**[0128]** In another embodiment, a suitable 1-hydroxyalkyl 2-bromo-substituted benzene (**2-1**) is reacted with a suitable 2,2-dialkoxy-ethanamine or *N*-protected 2,2-dialkoxy-ethanamine (**2-2**) in the presence of an acid or a Lewis acid such as trifluoromethanesulfonic acid or trimethylsilyl trifluoromethanesulfonate to render the cyclized product (**2-3**) (Scheme 2).  $\text{Pd-C}$  catalyzed hydrodehalogenation of **2-3** affords compound **I**, which may be separated using chiral HPLC to provide single enantiomers of formula (**I**). In some cases, **2-3** is first *N*-protected with a BOC group followed by hydrodehalogenation and deprotection to provide compound **I**, which may be separated using chiral HPLC to provide single enantiomers of formula (**I**).

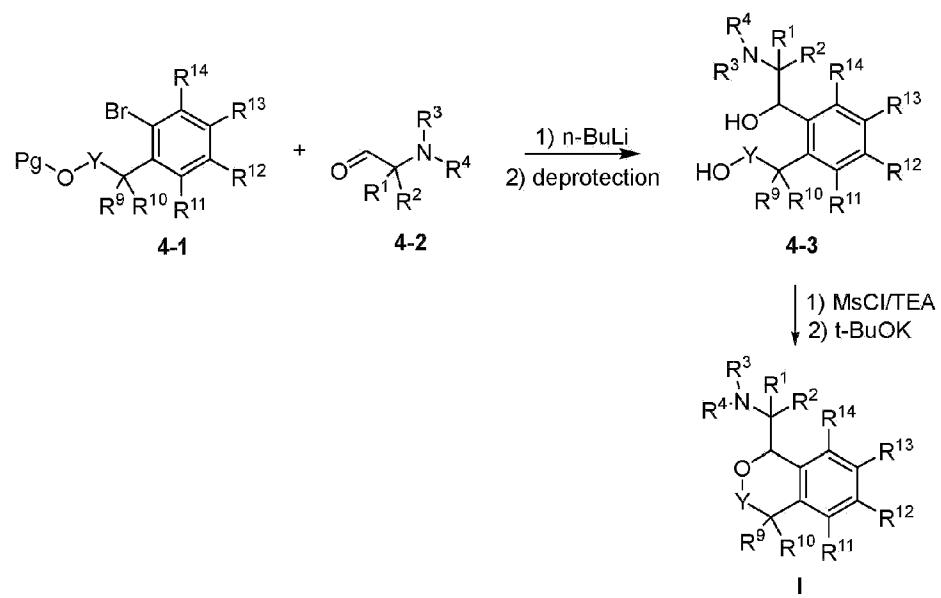
Scheme 3





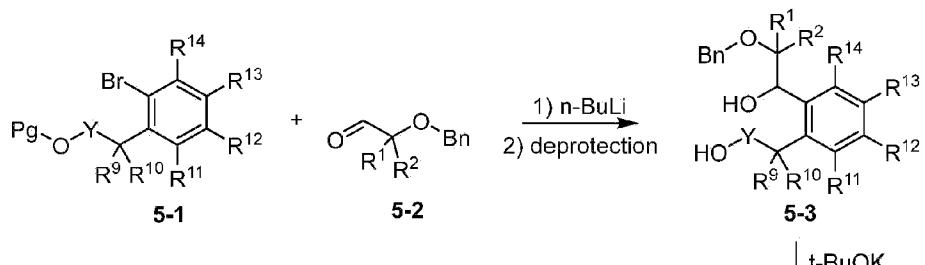
[0129] In another embodiment, a suitable hydroxyl-1-chloro-alkyl substituted benzene (**3-1**) is reacted with a suitable 2,2-dialkoxy-ethanamine or N-protected 2,2-dialkoxy-ethanamine (**3-2**) in the presence of an acid or a Lewis acid such as trifluoromethanesulfonic acid or trimethylsilyl trifluoromethanesulfonate to render the cyclized product (**3-3**, or **I** where  $R^9 = Cl$ ) (Scheme 3). Treatment of **3-3** with silver nitrate followed by zinc powder in acetic acid affords the hydroxyl compound **3-4**, or **I** where  $R^9 = OH$ , which is converted to compound **I** ( $R^9 = F$ ) with a fluorinating reagent such as BAST. The stereoisomers of **I** are separated using HPLC/chiral HPLC to provide single enantiomers of formula (**I**).

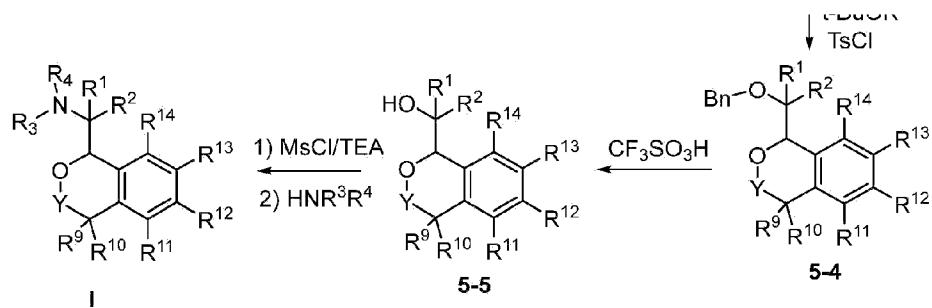
**Scheme 4**



[0130] In another embodiment, a suitable O-protected hydroxylalkyl substituted bromobenzene (**4-1**) is treated with a lithium reagent such as *n*-BuLi, followed by reaction with an aminoacetaldehyde or an *N*-protected aminoacetaldehyde (**4-2**) and then removal of the O-protecting group to give compound **4-3** (Scheme 4). Treatment of **4-3** with methanesulfonyl chloride and TEA, followed by reaction with *t*-BuOK provides compound I, which is separated using chiral HPLC to provide single enantiomers of formula (I).

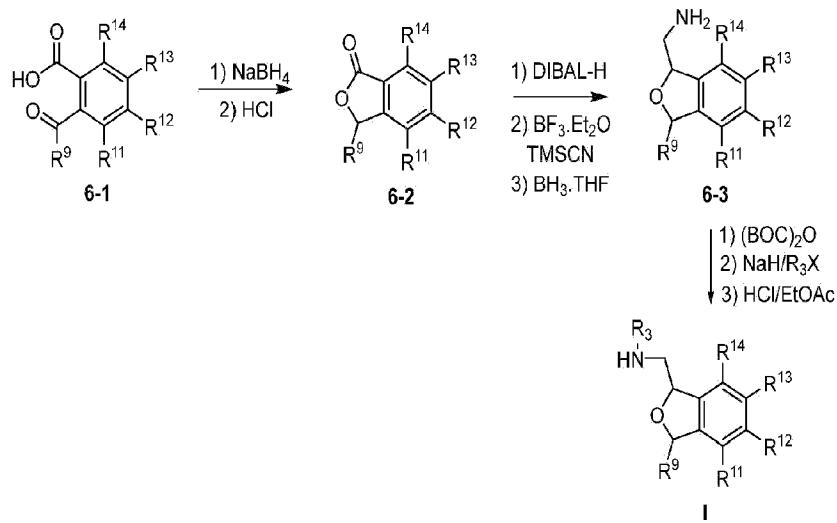
**Scheme 5**





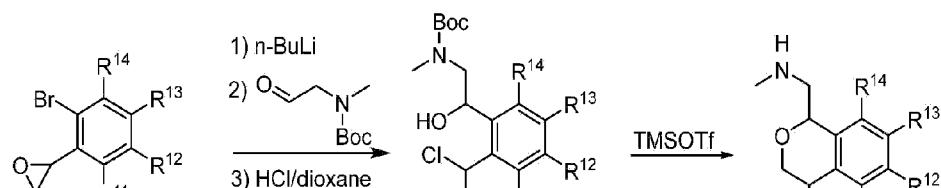
**[0131]** In another embodiment, a suitable O-protected hydroxylalkyl substituted bromobenzene (**5-1**) is treated with a lithium reagent such as *n*-BuLi, followed by reaction with a suitable O-protected hydroxyacetaldehyde (**5-2**) and then selective removal of the O-protecting group (Pg) to give compound **5-3** (Scheme 5). Treatment of **5-3** with 4-toluenesulfonyl chloride and *t*-BuOK provides cyclized compound **5-4**, which is reacted with trifluoromethanesulfonic acid to remove the benzyl protecting group to afford compound **5-5**. Compound **I** is produced by treating **5-5** with MsCl/TEA, followed by reaction with a suitable amine. **I** is separated using chiral HPLC to provide single enantiomers of formula (**I**).

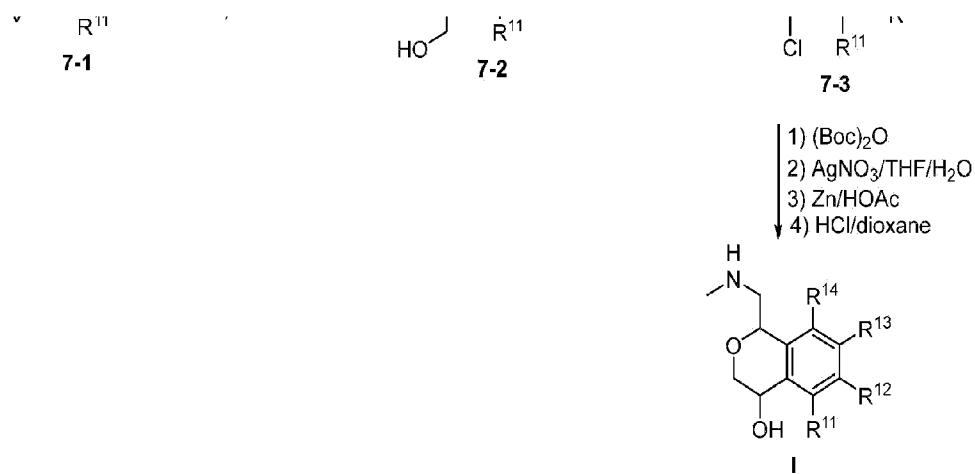
Scheme 6



**[0132]** In another embodiment, a suitable 2-acyl-substituted benzoic acid (**6-1**) is reacted with sodium borohydride, followed by ring closure in the presence of an acid to give isobenzofuran-1(3H)-one (**6-2**). Isobenzofuran-1(3H)-yl-methanamine (**6-3**) was prepared using standard methodologies *via* isobenzofuran-1(3H)-carbonitrile intermediate. Reaction of **6-3** with di-*tert*-butyldicarbonate, followed by alkylation and deprotection, gave compound **I**. The stereoisomers of **I** are separated using HPLC/chiral HPLC to provide single enantiomers (**I**).

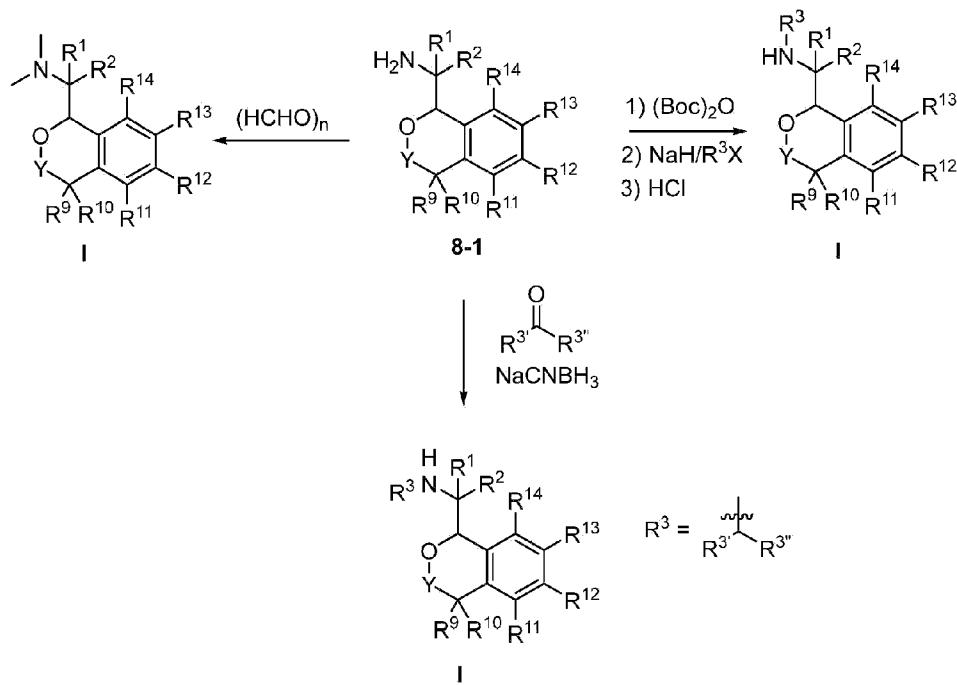
Scheme 7





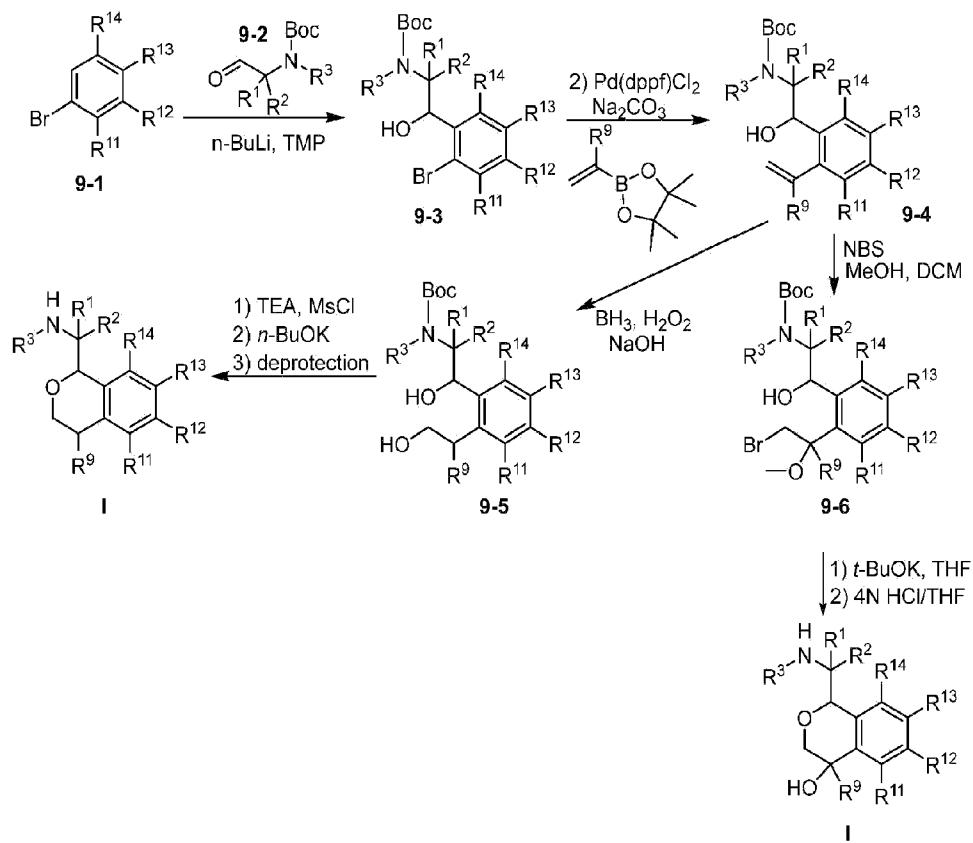
**[0133]** In another embodiment, a suitable 2-(2-bromophenyl)oxirane (**7-1**) is reacted with *n*-BuLi and *tert*-butyl methyl(2-oxoethyl)carbamate, followed by treatment with HCl to form intermediate **7-2**. Treatment of **7-2** with TMS trifluoromethanesulphonate yields 1-(4-chloroisochroman-1-yl)-*N*-methylmethanamine (**7-3**, or **I** where R<sup>9</sup> = Cl). Treatment of Boc-protected **7-3** with silver nitrate followed by zinc powder in acetic acid converts the chloride to the corresponding hydroxide. Removal of the protecting Boc-group affords compound **I**. The stereoisomers of **I** are separated using HPLC/chiral HPLC to provide single enantiomers (**I**).

Scheme 8



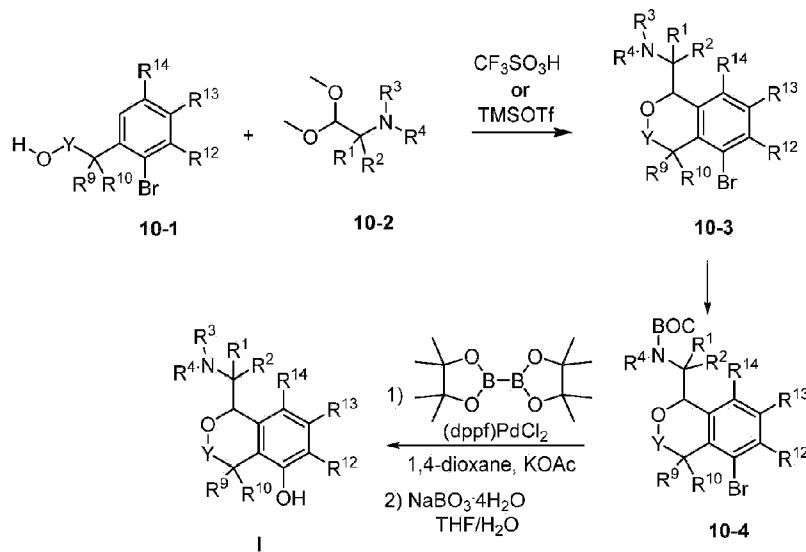
**[0134]** In another embodiment, a suitable *N*-unsubstituted compound **I** (**8-1**) can be alkylated to give compounds of formula **I** by direct alkylation with an alkyl halide *via* its Boc-protected intermediate or by reductive amination using a ketone or an aldehyde. The stereoisomers of **I** are separated using HPLC/chiral HPLC to provide single enantiomers (**I**).

Scheme 9



**[0135]** In another embodiment, a suitable aryl bromide (**9-1**) is reacted with *n*-BuLi and a suitable *N*-protected aminoacetaldehyde **9-2** to form intermediate **9-3**. Coupling of **9-3** with a suitable vinyl-1,3,2-dioxaborolane such as 3,3,4,4-tetramethyl-1-vinylborolane provides **9-4**. Hydroboration-oxidation of **9-4** yields **9-5**. Mesylation, cyclization, then BOC-deprotection affords compound **I**. Alternatively, bromination of **9-4** yields **9-6**, which is cyclized and deprotected to yield **I**. The stereoisomers of **I** are separated using HPLC/chiral HPLC to provide single enantiomers (**I**).

**Scheme 10**



[0136] In another embodiment, a suitable 1-hydroxyalkyl 2-bromo-substituted benzene (**10-1**) is reacted with a suitable 2,2-dialkoxy-ethanamine or *N*-protected 2,2-dialkoxy-ethanamine (**10-2**) in the presence of an acid or a Lewis acid such as trifluoromethanesulfonic acid or trimethylsilyl trifluoromethanesulfonate to render the cyclized product (**10-3**) (Scheme 10). Protection of **10-3** followed by Pd-catalyzed borylation then treatment with sodium perborate affords compound I, which may be separated using chiral HPLC to provide single enantiomers of formula (I). In some cases, **2-3** is first *N*-protected with a BOC group followed by hydrodehalogenation and deprotection to provide compound I, which may be separated using chiral HPLC to provide single enantiomers of formula (I).

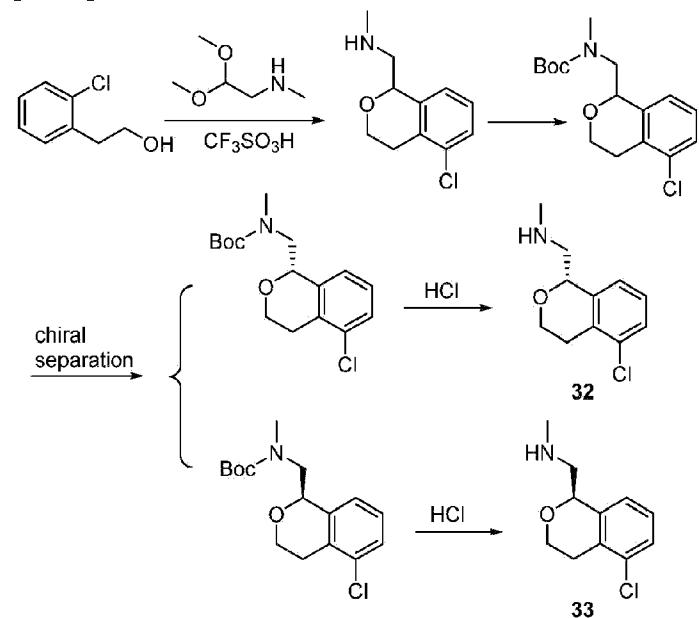
#### Examples 1-114

[0137] Representative compounds of the invention were prepared in the following Examples utilizing the general schemes above and procedures below.

#### General Procedure A:

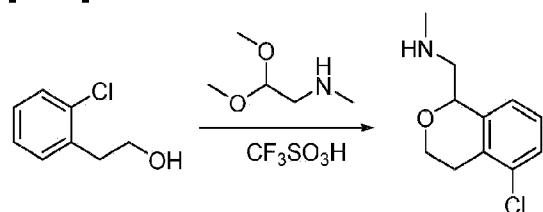
#### **1.1 Preparation of (*S*)-1-(5-chloroisochroman-1-yl)-*N*-methylmethanamine (**32**) and (*R*)-1-(5-chloroisochroman-1-yl)-*N*-methylmethanamine (**33**)**

[0138]



#### **(a). 1-(5-chloroisochroman-1-yl)-*N*-methylmethanamine**

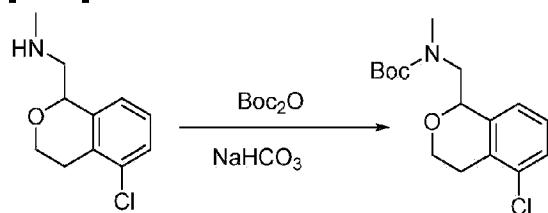
[0139]



[0140] To a solution of 2-(2-chlorophenyl)ethanol (3 g, 19.1 mmol) in dichloromethane (15 mL) was added 2,2-dimethoxy-N-methylethanamine (4.55 g, 25.4 mmol) and trifluoromethanesulfonic acid (8.4 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h. Trifluoromethanesulfonic acid (8.4 mL) was added at 0 °C again. The reaction was stirred at ambient temperature for an additional 2 h. The mixture was neutralized with 2N sodium hydroxide (aq.) to pH=8, extracted with dichloromethane ( $3 \times 150$  mL). The organic layer was dried over sodium sulfate, filtered and then concentrated to give the crude product which was used for next step without further purification.

**(b). *tert*-butyl (5-chloroisochroman-1-yl)methyl(methyl)carbamate**

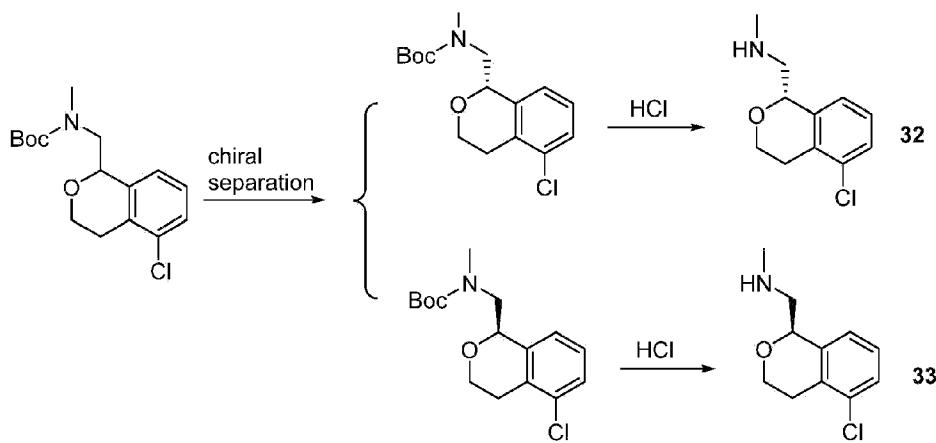
[0141]



[0142] To a solution of 1-(5-chloroisochroman-1-yl)-*N*-methylmethanamine (9.31 g, 44 mmol) in tetrahydrofuran (100 mL) was added di-*tert*-butyl dicarbonate (19.2 g, 88.0 mmol) and sodium bicarbonate (11.0 g, 132 mmol). The reaction was stirred at ambient temperature for 2 h. Upon the completion, the mixture was extracted with dichloromethane ( $80 \text{ mL} \times 3$ ). The organic layer was dried over sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (petroleum ether:ethyl acetate= 10:1) to give *tert*-butyl ((5-chloroisochroman-1-yl)methyl) (methyl)carbamate (13 g) as yellow oil.

**(c). (S)-1-(5-chloroisochroman-1-yl)-*N*-methylmethanamine (32) and (R)-1-(5-chloroisochroman-1-yl)-*N*-methylmethanamine (33)**

[0143]



**[0144]** *tert*-butyl ((5-chloroisochroman-1-yl)methyl)(methyl)carbamate (1 g) was separated by chiral HPLC: IC 20×250 mm, Sum (Dacel), mobile phase: CO<sub>2</sub>/ IPA{0.2% Ammonia (7M methanal)}= 85/15, flow rate: 80 g/min, back pressure: 100 bar, cycle time: 4.7 min to give (S)-*tert*-butyl ((5-chloroisochroman-1-yl)methyl)(methyl)carbamate (350 mg) and (R)-*tert*-butyl ((5-chloroisochroman-1-yl)methyl)(methyl)carbamate (350 mg) as colorless oil.

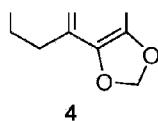
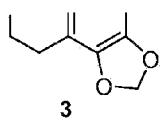
**[0145]** To a solution of (S)-*tert*-butyl ((5-chloroisochroman-1-yl)methyl) (methyl)carbamate (320 mg, 1.02 mmol) in ethyl acetate (1 mL) was added HCl/MeOH (733 mg, 20.4 mmol) at 0°C. The reaction was stirred at ambient temperature for 16 h. Upon the completion, the mixture was concentrated to give the HCl salt of **32** (0.22 g) as a white solid. ESI: m/z= 212 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.39 (d, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 5.11-5.09 (m, 1H), 4.31-4.27 (m, 1H), 3.91-3.86 (m, 1H), 3.64 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.36 - 3.34 (m, 1H), 2.98 - 2.85 (m, 2H), 2.79 (s, 3H).

**[0146]** To a solution of (R)-*tert*-butyl ((5-chloroisochroman-1-yl)methyl) (methyl)carbamate (320 mg, 1.02 mmol) in ethyl acetate (10 mL) was added HCl/MeOH (733 mg, 20.4 mmol) at 0°C. The reaction was stirred at ambient temperature for 16 h. Upon the completion, the mixture was concentrated to give the HCl salt of **33** (0.22 g) as a white solid. ESI: m/z = 212 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.39 (d, *J* = 8 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 5.11-5.09 (m, 1H), 4.31-4.27 (m, 1H), 3.91-3.86 (m, 1H), 3.64 (dd, *J* = 12.9, 3.0 Hz, 1H), 3.36 - 3.34 (m, 1H), 2.96 - 2.85 (m, 2H), 2.79 (s, 3H).

## 1.2 Preparation of (S)-1-(8,9-dihydro-6H-[1,3]dioxolo[4,5-]isochromen-6-yl)-N-methylmethanamine (3) and (R)-1-(8,9-dihydro-6H-[1,3]dioxolo[4,5-f]isochromen-6-yl)-N-methylmethanamine (4) (reference examples)

**[0147]**





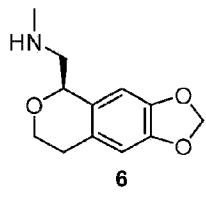
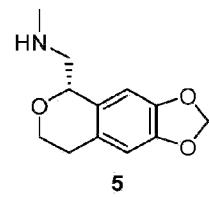
**[0148]** (S)-1-(8,9-dihydro-6H-[1,3]dioxolo[4,5-f]isochromen-6-yl)-N-methylmethanamine (**3**) and (R)-1-(8,9-dihydro-6H-[1,3]dioxolo[4,5-f]isochromen-6-yl)-N-methyl-methanamine (**4**) were prepared using General Procedure A and Scheme 1 starting with 2-(benzo[*d*][1,3]dioxol-4-yl)ethan-1-ol and 2,2-dimethoxy-*N*-methylethanamine.

**[0149]** (S)-1-(8,9-dihydro-6H-[1,3]dioxolo[4,5-f]isochromen-6-yl)-N-methylmethanamine (**3**) :  
MS (ESI): m/z 222.1 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-d6, HCl salt) δ 8.87 (bs, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 3.2 Hz, 2 H), 5.00 (d, *J* = 8.0 Hz, 1 H), 4.05-4.10 (m, 1 H), 3.72-3.78 (m, 1 H), 3.48-3.45 (m, 1H), 3.21-3.15 (m, 1 H), 2.61-2.71 (m, 2 H), 2.57 (s, 3 H).

**[0150]** (R)-1-(8,9-dihydro-6H-[1,3]dioxolo[4,5-f]isochromen-6-yl)-N-methyl-methanamine (**4**) :  
MS (ESI): m/z 222.1 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-d6, HCl salt) δ 8.66 (bs, 1 H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 3.2 Hz, 2 H), 5.01 (d, *J* = 8.6 Hz, 1 H), 3.72-3.78 (m, 1 H), 4.05-4.10 (m, 1 H), 3.48-3.45 (m, 1H), 3.21-3.15 (m, 1H), 2.61-2.75 (m, 2 H), 2.57 (s, 3 H).

**1.3 Preparation of (S)-1-(7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochromen-5-yl)-N-methylmethanamine (**5**) and (R)-1-(7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochromen-5-yl)-N-methylmethanamine (**6**) (reference examples)**

**[0151]**



**[0152]** (S)-1-(7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochromen-5-yl)-N-methylmethanamine (**5**) and (R)-1-(7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochromen-5-yl)-N-methylmethanamine (**6**) were prepared using General Procedure A and Scheme 1 starting with 2-(benzo[*d*][1,3]dioxol-5-yl)ethanol and 2,2-dimethoxy-*N*-methylethanamine.

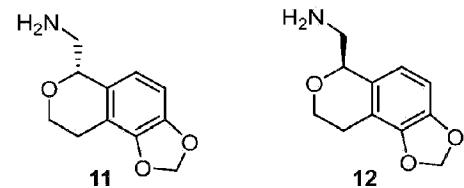
**[0153]** (S)-1-(7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochromen-5-yl)-N-methylmethanamine (**5**) :  
MS ESI: m/z=222[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 6.70 (s, 1H), 6.68 (s, 1H), 5.93 (d, *J* = 1.2 Hz, 2H), 4.97 (d, *J*= 7.3 Hz, 1H), 4.18-4.13 (m, 1H), 3.81~3.75 (m, 1H), 3.54~3.50 (dd, *J*<sub>1</sub> = 12.9, *J*<sub>2</sub>=2.8 Hz, 1H), 3.28~3.25 (m, 1H), 2.91~2.87 (m, 1H), 2.75 (s, 3H),

2.8~2.62 (m, 1H).

**[0154]** (*R*)-1-(7,8-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isochromen-5-yl)-*N*-methylmethanamine (**6**) :  
MS (ESI): m/z=222[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.58 (s, 1H), 6.57 (s, 1H), 5.90~5.89 (m, 2H), 4.79~4.77 (d, *J* = 6.4 Hz, 1H), 4.11~4.07 (m, 1H), 3.76~3.70 (m, 1H), 2.96~2.81 (m, 3H), 2.61~2.57 (m, 1H), 2.48 (s, 3H).

**1.4 Preparation of (*S*)-(8,9-dihydro-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-yl)methanamine (**11**) and (*R*)-(8,9-dihydro-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-yl)methanamine (**12**) (reference examples)**

**[0155]**



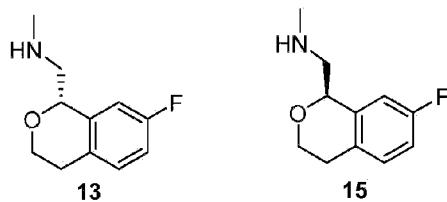
**[0156]** (*S*)-(8,9-dihydro-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-yl)methanamine **11** and (*R*)-(8,9-dihydro-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-yl)methanamine **12** were prepared using General Procedure A and Scheme 1 starting with 2-(benzo[*d*][1,3]dioxol-4-yl)ethanol and 2,2-dimethoxyethanamine in the presence of trimethylsilyl trifluoromethanesulfonate instead of trifluoromethanesulfonic acid.

**[0157]** (*S*)-(8,9-dihydro-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-yl)methanamine (**11**): MS (ESI): m/z=208[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 6.76~6.74 (d, *J* = 8.1 Hz, 1H), 6.69~6.67 (d, *J* = 8.1 Hz, 1H), 5.979 (s, 2H), 4.95~4.93 (dd, *J*<sub>1</sub>= 8.6, *J*<sub>2</sub>=2.2 Hz, 1H), 4.23~4.18 (m, 1H), 3.83~3.76 (m, 1H), 3.49~3.45 (dd, *J*<sub>1</sub>= 13.1, *J*<sub>2</sub>=3.1 Hz, 1H), 3.20~3.15 (m, 1H), 2.84~2.80 (m, 1H), 2.73~2.68 (dt, *J*<sub>1</sub>=16.6, *J*<sub>2</sub>=3.5 Hz, 1H).

**[0158]** (*R*)-(8,9-dihydro-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-yl)methanamine (**12**): MS (ESI): m/z=208[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 6.76~6.74 (d, *J* = 8.1 Hz, 1H), 6.70~6.68 (d, *J* = 8.2 Hz, 1H), 5.977 (s, 2H), 4.96~4.93 (dd, *J*<sub>1</sub>= 8.6, *J*<sub>2</sub>=2.2 Hz, 1H), 4.23~4.18 (m, 1H), 3.83~3.76 (m, 1H), 3.50~3.46 (dd, *J*<sub>1</sub>= 13.1, *J*<sub>2</sub>=3.1 Hz, 1H), 3.20~3.15 (m, 1H), 2.84~2.80 (m, 1H), 2.73~2.68 (dt, *J*<sub>1</sub>=16.6, *J*<sub>2</sub>=3.5 Hz, 1H).

**1.5 Preparation of (*S*)-1-(7-fluoroisochroman-1-yl)-*N*-methylmethanamine (**13**) and (*R*)-1-(7-fluoroisochroman-1-yl)-*N*-methylmethanamine (**15**)**

[0159]



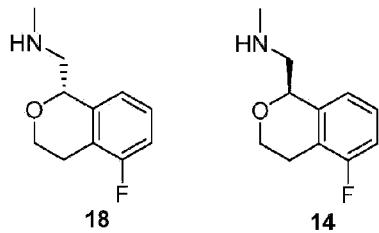
[0160] (*S*)-1-(7-fluoroisochroman-1-yl)-*N*-methylmethanamine (**13**) and (*R*)-1-(7-fluoroisochroman-1-yl)-*N*-methylmethanamine (**15**) were prepared using General Procedure A and Scheme 1 starting with 2-(4-fluorophenyl)ethanol and 2,2-dimethoxy-*N*-methylethanamine.

**[0161]** (S)-1-(7-fluoroisochroman-1-yl)-N-methylmethanamine (**13**): MS (ESI)  $m/z$ =196[M+H]<sup>+</sup>.  $^1\text{H}$  NMR (400 MHz, CD<sub>3</sub>OD, HCl salt)  $\delta$  7.25~7.23 (m, 1H), 7.03~6.98 (m, 2H), 5.09~5.07 (m, 1H), 4.245~4.21 (m, 1H), 3.86~3.82 (m, 1H), 3.63~3.60 (dd,  $J_1 = 12.9$ ,  $J_2=3.2$  Hz, 1H), 3.35~3.32 (m, 1H), 3.03~2.95 (m, 1H), 2.78 (s, 3H), 2.74-2.72 (m 1H).

**[0162] (R)-1-(7-fluoroisochroman-1-yl)-N-methylmethanamine (15):** MS (ESI): m/z=196[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.26~7.23 (m, 1H), 7.04~7.01 (m, 2H), 5.09~5.07 (m, 1H), 4.245~4.21 (m, 1H), 3.87~3.82 (m, 1H), 3.63~3.60 (dd,  $J_1 = 12.9$ ,  $J_2 = 3.2$  Hz, 1H), 3.356~3.34 (m, 1H), 3.03~2.95 (m, 1H), 2.78 (s, 3H), 2.74~2.72 (m 1H).

### 1. 6 Preparation of (S)-1-(5-fluoroisochroman-1-yl)-N-methylmethanamine (18) and (R)-1-(5-fluoroisochroman-1-yl)-N-methylmethanamine (14)

[0163]



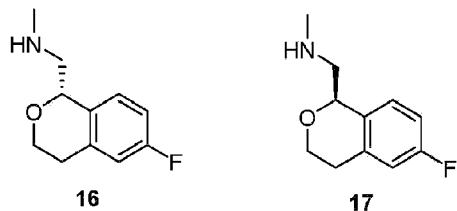
[0164] (*S*)-1-(5-fluoroisochroman-1-yl)-*N*-methylmethanamine (**18**) and (*R*)-1-(5-fluoroisochroman-1-yl)-*N*-methylmethanamine (**14**) were prepared using General Procedure A and Scheme 1 starting with 2-(2-fluorophenyl)ethanol and 2,2-dimethoxy-*N*-methylmethanamine.

**[0165] (S)-1-(S-fluoroisochroman-1-yl)-N-methyl-methanamine (18):** MS (ESI) : m/z 196 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.31-7.26 (m, 1H), 7.07 - 7.01 (m, 2H), 5.11-5.09 (m, 1H), 4.28-4.23 (m, 1H), 3.88-3.82 (m, 1H), 3.66-3.62 (m, 1H), 3.37 - 3.30 (m, 1H), 2.89 - 2.83 (m, 2H), 2.77 (s, 3H).

**[0166] (R)-1-(5-fluoroisochroman-1-yl)-N-methylmethanamine (14):** MS (ESI): m/z= 196 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.31-7.26 (m, 1H), 7.06 - 7.02 (m, 2H), 5.10 (d, *J* = 8.5 Hz, 1H), 4.28-4.23 (m, 1H), 3.88-3.82 (m, 1H), 3.63 (dd, *J* = 12.9, 3.2 Hz, 1H), 3.37 - 3.33 (m, 1H), 2.96 - 2.79 (m, 2H), 2.77 (s, 3H).

### 1. 7 Preparation of (S)-1-(6-fluoroisochroman-1-yl)-N-methylmethanamine (16) and (R)-1-(6-fluoroisochroman-1-yl)-N-methylmethanamine (17)

[0167]



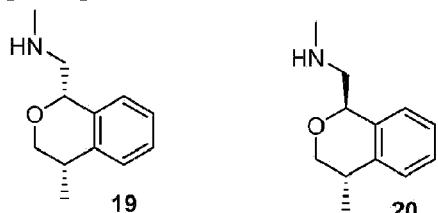
[0168] (S)-1-(6-fluoroisochroman-1-yl)-*N*-methylmethanamine (**16**) and (R)-1-(6-fluoroisochroman-1-yl)-*N*-methylmethanamine (**17**) were prepared using General Procedure A and Scheme 1 starting with 2-(3-fluorophenyl)ethanol and 2,2-dimethoxy-*N*-methylethanamine.

[0169] (S)-1-(6-fluoroisochroman-1-yl)-N-methylmethanamine (**16**): MS (ESI):  
 m/z=196[M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.25-7.21(m, 1H), 7.03~6.97(m, 2H), 5.08(d, *J* = 8.8 Hz, 1H), 4.23~4.18(m, 1H), 3.87~3.81(m, 1H), 3.61~3.57(m, 1H), 3.31~3.27(m, 1H), 3.06~2.98(m, 1H), 2.81~2.76(m, 4H).

**[0170] (R)-1-(6-fluoroisochroman-1-yl)-N-methylmethanamine (17):** MS (ESI): m/z=196[M+H]<sup>+</sup>.  
<sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.27-7.21(m, 1H), 7.02~6.97(m, 2H), 5.09(d, J= 8.0 Hz, 1H), 4.23~4.18(m, 1H), 3.87-3.81(m, 1H), 3.62~3.58(m, 1H), 3.31~3.27(m, 1H), 3.06~2.98(m, 1H), 2.81~2.75(m, 4H).

### 1.8 Preparation of *N* methyl 1-((1*S*,4*S*)-4-methylisochroman-1-yl)methanamine (19) and *N*-methyl-1-((1*R*,4*S*)-4-methylisochroman-1-yl)methanamine (20) (reference examples)

[0171]



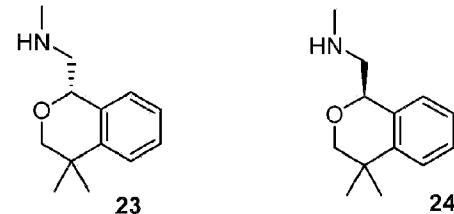
**[0172]** *N*-methyl-1-((1*S*,4*S*)-4-methylisochroman-1-yl)methanamine (**19**) and *N*-methyl-1-((1*R*,4*S*)-4-methylisochroman-1-yl)methanamine (**20**) were prepared using General Procedure A and Scheme 1 starting with (S)-2-phenylpropan-1-ol and 2,2-dimethoxy-*N*-methylethanamine.

**[0173]** *N*-methyl-1-((1*S*,4*S*)-4-methylisochroman-1-yl)methanamine (**19**): MS (ESI) m/z: 192 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.30 - 7.25 (m, 3H), 7.18 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 9.4, 3.1 Hz, 1H), 3.99-3.92 (m, 2H), 3.68-3.65 (m, 1H), 3.31 - 3.27 (m, 1H), 2.92 - 2.86 (m, 1H), 2.79 (s, 3H), 1.39 (d, J = 7.1 Hz, 3H).

**[0174]** *N*-methyl-1-((1*R*,4*S*)-4-methylisochroman-1-yl)methanamine (**20**): MS (ESI) m/z: 192 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.38 (d, J = 7.5 Hz, 1H), 7.33-7.25 (m, 2H), 7.18 (d, J = 7.6 Hz, 1H), 5.12 (dd, J = 9.5, 2.9 Hz, 1H), 4.16 (dd, J = 11.3, 4.8 Hz, 1H), 3.60 - 3.51 (m, 2H), 3.35-3.32 (m, 1H), 3.07-3.04 (m, 1H), 2.78 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H).

**1.9 Preparation of (S)-1-(4,4-dimethylisochroman-1-yl)-*N*-methylmethanamine (**23**) and (R)-1-(4,4-dimethylisochroman-1-yl)-*N*-methylmethanamine (**24**) (reference examples)**

**[0175]**



**[0176]** (S)-1-(4,4-dimethylisochroman-1-yl)-*N*-methylmethanamine (**23**) and (R)-1-(4,4-dimethylisochroman-1-yl)-*N*-methylmethanamine (**24**) were prepared using General Procedure A and Scheme 1 starting with 2-methyl-2-phenylpropan-1-ol and *tert*-butyl (2,2-dimethoxyethyl) (methyl)carbamate.

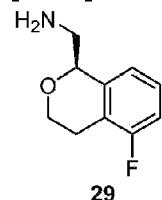
**[0177]** (S)-1-(4,4-dimethylisochroman-1-yl)-*N*-methylmethanamine (**23**): MS (ESI) m/z: 206 [M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt): δ 7.46 (d, J = 7.8 Hz, 1H), 7.34 - 7.12 (m, 3H), 5.11 (d, J = 9.8 Hz, 1H), 3.81 (d, J = 11.3 Hz, 1H), 3.68 - 3.55 (m, 2H), 3.31 - 3.27 (m, 1H), 2.79 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H).

**[0178]** (R)-1-(4,4-dimethylisochroman-1-yl)-*N*-methylmethanamine (**24**): MS (ESI) m/z: 206 [M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt): δ 7.46 (d, J = 7.8 Hz, 1H), 7.34 - 7.12 (m, 3H), 5.11 (d, J = 9.8 Hz, 1H), 3.81 (d, J = 11.3 Hz, 1H), 3.68 - 3.55 (m, 2H), 3.31 - 3.27 (m,

1H), 2.79 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H).

### 1.10 Preparation of (R)-(5-fluoroisochroman-1-yl)methanamine (29)

[0179]

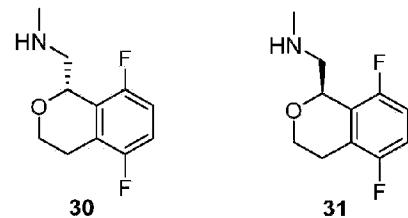


[0180] *(R)*-(5-fluoroisochroman-1-yl)methanamine (**29**) was prepared using General Procedure A and Scheme 1 starting with 2-(2-fluorophenyl) ethanol and 2,2-dimethoxyethanamine.

**[0181]** (*R*)-(5-fluoroisochroman-1-yl)methanamine (**29**): MS (ESI) m/z: 182 [M+H]<sup>+</sup>, <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.32~7.27 (m, 1H), 7.06~7.03 (m, 2H), 5.04~5.02 (m, 1H), 4.28~4.24 (m, 1H), 3.87~3.82 (m, 1H), 3.57~3.54 (dd, *J*<sub>1</sub> = 13.1, *J*<sub>2</sub> = 3.2 Hz, 1H), 3.26~3.21 (m, 1H), 2.90~2.87 (m, 1H), 2.83~2.80 (m, 1H).

### 1.11 Preparation of (S)-1-(5,8-difluoroisochroman-1-yl)-N-methylmethanamine (30) and (R)-1-(5,8-difluoroisochroman-1-yl)-N-methylmethanamine (31)

[0182]



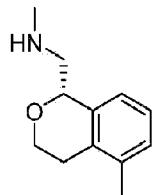
[0183] (S)-1-(S,8-difluoroisochroman-1-yl)-N-methylmethanamine (**30**) and (R)-1-(5,8-difluoroisochroman-1-yl)-N-methylmethanamine (**31**) were prepared using General Procedure A and Scheme 1 starting with 2-(2,5-difluorophenyl)ethanol and 2,2-dimethoxy-N-methylethanamine.

**[0184] (S)-1-(S,8-difluoroisochroman-1-yl)-N-methylmethanamine (30):** MS (ESI) m/z: 214 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.15-7.05 (m, 2H), 5.27-5.25 (m, 1H), 4.22 - 4.17 (m, 1H), 3.92-3.87 (m, 1H), 3.59-3.56 (m, 1H), 3.50 - 3.42 (m, 1H), 2.85 (t, J = 5.5 Hz, 2H), 2.80 (s, 3H).

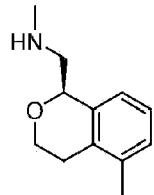
**[0185] (R)-1-(5,8-difluoroisochroman-1-yl)-N-methylmethanamine (31):** MS (ESI) m/z: 214 [M+H]<sup>+</sup>, <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt),  $\delta$  7.15-7.05 (m, 2H), 5.26-5.25 (m, 1H), 4.22 - 4.17 (m, 1H), 3.92-3.87 (m, 1H), 3.59-3.56 (m, 1H), 3.47 - 3.43 (m, 1H), 2.87-2.84 (m, 2H), 2.80 (s, 3H).

### 1.12 Preparation of (S)-N-methyl-1-(5-methylisochroman-1-yl)methanamine (38) and (R)-N-methyl-1-(5-methylisochroman-1-yl)methanamine (39)

[0186]



38



39

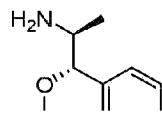
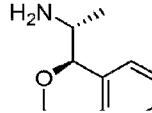
[0187] (S)-*N*-methyl-1-(5-methylisochroman-1-yl)methanamine (**38**) and (*R*)-*N*-methyl-1-(5-methylisochroman-1-yl)methanamine (**39**) were prepared using General Procedure A and Scheme 1 starting with 2-(*o*-tolyl)ethan-1-ol and 2,2-dimethoxy-*N*-methylethanamine.

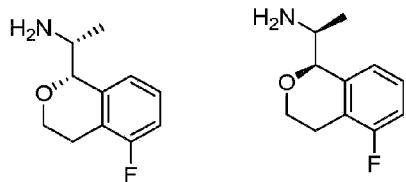
**[0188]** (*S*)-*N*-methyl-1-(5-methylisochroman-1-yl)methanamine (**38**): MS (ESI) m/z: 192[M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.18 - 7.12 (m, 2H), 7.04 - 7.02 (m, 1H), 5.09-5.06 (m, 1H), 4.28-4.23 (m, 1H), 3.89-3.83 (m, 1H), 3.61-3.57 (m, 1H), 3.31 - 3.26 (m, 1H), 2.85 - 2.81(m, 1H), 2.76 (s, 3H), 2.72-2.67 (m, 1H), 2.27 (s, 3H).

**[0189] (R)-N-methyl-1-(5-methylisochroman-1-yl)methanamine (39):** MS (ESI)  $m/z$ : 192 [M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt)  $\delta$  7.18 - 7.12 (m, 2H), 7.05 - 7.03 (m, 1H), 5.09-5.07 (m, 1H), 4.28-4.23 (m, 1H), 3.89-3.83 (m, 1H), 3.61-3.57 (m, 1H), 3.31 - 3.26 (m, 1H), 2.88 - 2.81 (m, 1H), 2.76 (s, 3H), 2.72-2.66 (m, 1H), 2.27 (s, 3H).

1.13 Preparation of compounds (42), (43), (52), and (53): ((R)-1-((R)-5-fluoroisochroman-1-yl)ethan-1-amine, ((S)-1-((S)-5-fluoroisochroman-1-yl)ethan-1-amine, (R)-1-((S)-5-fluoroisochroman-1-yl)ethan-1-amine and (S)-1-((R)-5-fluoroisochroman-1-yl)ethan-1-amine, order unknown

[0190]





(42), (43), (52), (53)

**[0191]** ((*R*)-1-((*R*)-5-fluoroisochroman-1-yl)ethan-1-amine, ((*S*)-1-((*S*)-5-fluoroisochroman-1-yl)ethan-1-amine, (*R*)-1-((*S*)-5-fluoroisochroman-1-yl)ethan-1-amine and (*S*)-1-((*R*)-5-fluoroisochroman-1-yl)ethan-1-amine were prepared using General Procedure A and Scheme 1 starting with 2-(2-fluorophenyl)ethan-1-ol and *tert*-butyl (1-oxopropan-2-yl)carbamate. All four stereoisomers were synthesized and characterized.

**[0192] (42):** MS (ESI) m/z: 196 (M+H)<sup>+</sup>, <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.36-7.32 (m, 1H), 7.16 (d, *J*=8 Hz, 1H), 7.09-7.06 (m, 1H), 4.89 (s, 1H), 4.36-4.33 (m, 1H), 3.98-3.94 (m, 1H), 3.80-3.75 (m, 1H), 2.94-2.80 (m, 2H), 1.55 - 1.54 (d, *J*=6.5 Hz, 3H).

**[0193] (43):** MS (ESI) m/z: 196 (M+H)<sup>+</sup>, <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.36-7.32 (m, 1H), 7.15 - 7.14 (d, *J*=7.5 Hz, 1H), 7.09-7.06 (m, 1H), 4.89 (s, 1H), 4.36-4.33 (m, 1H), 3.98-3.94 (m, 1H), 3.80-3.75 (m, 1H), 2.94-2.80 (m, 2H), 1.55 - 1.54 (d, *J*=7 Hz, 3H).

**[0194] (53):** MS (ESI) m/z: 196 (M+1)<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.33-7.28 (m, 1H), 7.07 - 7.02 (m, 2H), 5.07 (s, 1H), 4.38-4.33 (m, 1H), 4.01-3.96 (m, 1H), 3.79-3.72 (m, 1H), 2.88-2.79 (m, 2H), 1.05 - 1.04 (d, *J*=6.4 Hz, 3H).

**[0195] (52):** MS (ESI) m/z: 196 (M+1)<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.33-7.28 (m, 1H), 7.07 - 7.02 (m, 2H), 5.07 (s, 1H), 4.37-4.33 (m, 1H), 4.00-3.96 (m, 1H), 3.79-3.72 (m, 1H), 2.87-2.79 (m, 2H), 1.05 - 0.98 (m, 3H).

### 1.14 (*R*)-(6-fluoroisochroman-1-yl)methanamine (34)

**[0196]**

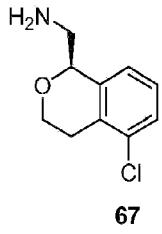
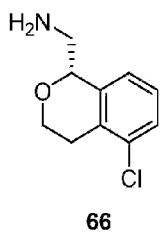


[0197] *(R)*-(6-fluoroisochroman-1-yl)methanamine (**34**) was prepared using General Procedure A and Scheme 1 starting with 2-(3-fluorophenyl)ethanol.

**[0198]** (R)-(6-fluoroisochroman-1-yl)methanamine (**34**): (ESI)m/z=182[M+H]<sup>+</sup>, <sup>1</sup>HNMR (500 MHz, CD<sub>3</sub>OD, HCl salt): 7.25~7.23 (m, 1 H), 7.03~7.00 (m, 2 H), 5.01 (d, J =9 Hz, 1 H), 4.23~4.19 (m, 1 H), 3.87~3.82 (m, 1 H), 3.51~3.55 (m, 1 H), 3.23~3.19 (m, 1 H), 3.07~3.00 (m, 1 H), 2.81~2.76 (m, 1H).

### 1.15 Preparation of (S)-(5-chloroisochroman-1-yl)methanamine (66) and (R)-(5-chloroisochroman-1-yl)methanamine (67)

[0199]



[0200] *(S)-(5-chloroisochroman-1I-yl)methanamine (66) and (R)-(5-chloroisochroman-1-yl)methanamine (67)* were prepared using General Procedure A and Scheme 1 starting with 2-(2-chlorophenyl)ethan-1-ol and 2,2-dimethoxyethanamine.

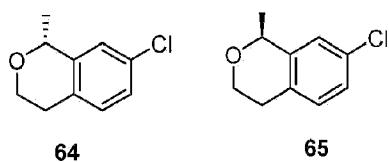
**[0201] (S)-(5-chloroisochroman-1-yl)methanamine (66):** MS (ESI) m/z: 198[M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.39 (d, J = 8 Hz, 1H), 7.28 (t, J = 8 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 5.04-5.02 (m, 1H), 4.30-4.25 (m, 1H), 3.90-3.84 (m, 1H), 3.58-3.54 (m, 1H), 3.26 - 3.21 (m, 1H), 2.99 - 2.84(m, 2H).

**[0202] (R)-(5-chloroisochroman-1-yl)methanamine (67):** MS (ESI) m/z: 198[M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.39 (d, J = 8 Hz, 1H), 7.28 (t, J = 8 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 5.03-5.01 (m, 1H), 4.30-4.25 (m, 1H), 3.90-3.84 (m, 1H), 3.57-3.53 (m, 1H), 3.26 - 3.21 (m, 1H), 2.97 - 2.84(m, 2H).

### 1.16 Preparation of (S)-1-(7-chloroisochroman-1-yl)-N-methylmethanamine (64) and (R)-1-(7-chloroisochroman-1-yl)-N-methylmethanamine (65)

[0203]





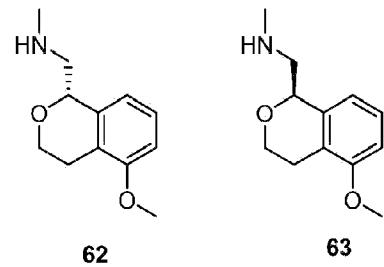
[0204] (S)-1-(7-chloroisochroman-1-yl)-N-methylmethanamine (**64**) and (R)-1-(7-chloroisochroman-1-yl)-N-methylmethanamine (**65**) were prepared using General Procedure A and Scheme 1 starting with 2-(4-chlorophenyl)ethan-1-ol and 2,2-dimethoxy-N-methylethanamine.

**[0205] (S)-1-(7-chloroisochroman-1-yl)-N-methylmethanamine (64):** MS (ESI) m/z: 212[M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.30-7.22 (m, 3H), 5.08-5.06 (m, 1H), 4.26-4.21 (m, 1H), 3.88-3.82 (m, 1H), 3.64-3.60 (m, 1H), 3.37 - 3.32 (m, 1H), 3.04 - 2.96 (m, 1H), 2.80-2.72 (m, 4H).

**[0206] (R)-1-(7-chloroisochroman-1-yl)-N-methylmethanamine (65):** MS (ESI) m/z: 212[M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.30-7.22 (m, 3H), 5.08-5.06 (m, 1H), 4.26-4.20 (m, 1H), 3.88-3.82 (m, 1H), 3.64-3.60 (m, 1H), 3.37 - 3.32 (m, 1H), 3.04 - 2.96 (m, 1H), 2.80-2.74 (m, 4H).

### 1.17 Preparation of (S)-1-(5-methoxyisochroman-1-yl)-N-methylmethanamine (62) and (R)-1-(5-methoxyisochroman-1-yl)-N-methylmethanamine (63) (reference examples)

[0207]



[0208] (S)-1-(5-methoxyisochroman-1-yl)-N-methylmethanamine (**62**) and (R)-1-(5-methoxyisochroman-1-yl)-N-methylmethanamine (**63**) were prepared using General Procedure A and Scheme 1 starting with 2-(2-methoxyphenyl)ethan-1-ol and 2,2-dimethoxy-N-methylethanamine.

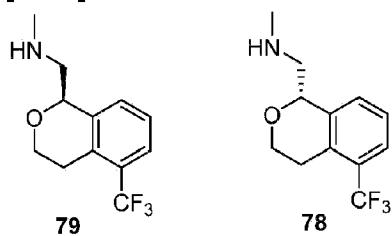
**[0209]** (S)-1-(5-methoxyisochroman-1-yl)-N-methylmethanamine (**62**): MS (ESI) m/z: 208[M+H]<sup>+</sup>, <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.25 (t, J = 8 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 5.07-5.04 (m, 1H), 4.26-4.21 (m, 1H), 3.86 (s, 3H), 3.84-3.79 (m,

1H), 3.62-3.58 (m, 1H), 3.32 - 3.29 (m, 1H), 2.79-2.77 (m, 5H).

**[0210] *R*)-1-(5-methoxyisochroman-1-yl)-*N*-methylmethanamine (63): MS (ESI) m/z: 208[M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.25 (t, J = 8 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 5.06-5.04 (m, 1H), 4.26-4.21 (m, 1H), 3.86 (s, 3H), 3.84-3.79 (m, 1H), 3.62-3.58 (m, 1H), 3.32 - 3.28 (m, 1H), 2.79-2.77 (m, 5H).**

### 1.18 Preparation of (R)-N-methyl-1-(5-(trifluoromethyl)isochroman-1-yl)- methanamine (79) and (S)-N-methyl-1-(5-(trifluoromethyl)isochroman-1-yl)- methanamine (78) (reference examples)

[0211]



[0212] (*R*)-*N*-methyl-1-(5-(trifluoromethyl)isochroman-1-yl)- methanamine (**79**) and (*S*)-*N*-methyl-1-(5-(trifluoromethyl)isochroman-1-yl)- methanamine (**78**) were prepared using General Procedure A and Scheme 1 starting with 2-(2-(trifluoromethyl)phenyl)ethanol and 2,2-dimethoxy-*N*-methylethanamine.

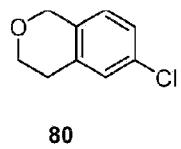
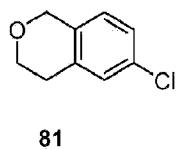
**[0213]** (*R*)-*N*-methyl-1-(5-(trifluoromethyl)isochroman-1-yl- methanamine (**79**): MS(ESI) m/z = 246 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  7.67 (d, *J* = 7.2 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 5.22- 5.20 (m, 1 H), 4.28- 4.23 (m, 1 H), 3.91-3.85 (m, 1 H), 3.68-3.64 (m, 1 H), 3.40-3.35 (m, 1 H), 3.16-3.08 (m, 1 H), 3.01-2.97 (m, 1 H), 2.80 (s, 3 H).

**[0214]** (S)-*N*-methyl-1-(5-(trifluoromethyl)isochroman-1-yl)- methanamine (**78**): MS(ESI) *m/z* = 246 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, methanol-*d*<sub>4</sub>)  $\delta$  7.67 (d, *J* = 7.2 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 5.22- 5.20 (m, 1 H), 4.28- 4.23 (m, 1 H), 3.91-3.85 (m, 1 H), 3.68- 3.64 (m, 1 H), 3.40-3.35 (m, 1 H), 3.16-3.08 (m, 1 H), 3.01-2.97 (m, 1 H), 2.80 (s, 3 H).

### 1.19 Preparation of (R)-1-(6-chloroisochroman-1-yl)-N-methylmethanamine (81) and (S)-1-(6-chloroisochroman-1-yl)-N-methylmethanamine (80)

[0215]





**[0216]** (*R*)-1-(6-chloroisochroman-1-yl)-*N*-methylmethanamine (**81**) and (*S*)-1-(6-chloroisochroman-1-yl)-*N*-methylmethanamine (**80**) were prepared using General Procedure A and Scheme 1 starting with 2-(3-chlorophenyl)ethanol and 2,2-dimethoxy-*N*-methylethanamine.

**[0217]** (*R*)-1-(6-chloroisochroman-1-yl)-*N*-methylmethanamine (**81**): MS (ESI): m/z= 212 [M + H]<sup>+</sup>.

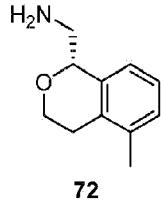
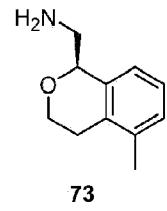
**[0218]** <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-d2): δ 7.21-7.18 (m, 2 H), 7.07-7.05 (m, 1 H), 5.07-5.04 (m, 1 H), 4.07-4.02 (m, 1 H), 3.79-3.73 (m, 1 H), 3.45-3.35 (m, 2 H), 2.89-2.81 (m, 1 H), 2.72-2.70 (m, 1 H), 2.65 (s, 3 H).

**[0219]** (*S*)-1-(6-chloroisochroman-1-yl)-*N*-methylmethanamine (**80**): MS (ESI): m/z= 212 [M+H]<sup>+</sup>.

**[0220]** <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-d2): δ 7.20-7.18 (m, 2 H), 7.07-7.05 (m, 1 H), 5.06-5.04 (m, 1 H), 4.07-4.02 (m, 1 H), 3.79-3.73 (m, 1 H), 3.45-3.35 (m, 2 H), 2.89-2.81 (m, 1 H), 2.72-2.70 (m, 1 H), 2.65 (s, 3 H).

**1.20 Preparation of (*R*)-(5-methylisochroman-1-yl)methanamine (**73**) and (*S*)-(5-methylisochroman-1-yl)methanamine (**72**)**

**[0221]**



**[0222]** (*R*)-(5-methylisochroman-1-yl)methanamine (**73**) and (*S*)-(5-methylisochroman-1-yl)methanamine (**72**) were prepared using General Procedure A and Scheme 1 starting with 2-(o-tolyl)ethanol and 2,2-dimethoxy-ethanamine.

**[0223]** (*R*)-(5-methylisochroman-1-yl)methanamine (**73**): (ESI)m/z: 178 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, MeOD-d<sub>4</sub>) δ 7.19-7.13 (m, 2 H), 7.04-7.02 (m, 1 H), 4.28-4.23 (m, 1 H), 3.90-3.84 (m, 1

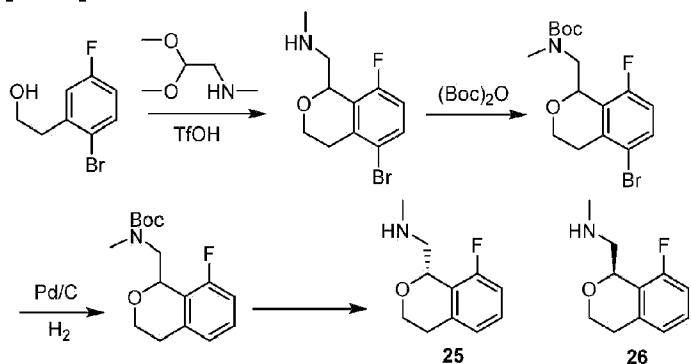
H), 3.54-3.50 (dd,  $J$ = 3.2, 13.2 Hz, 1 H), 3.22-3.16 (dd,  $J$ = 9.2, 13.2 Hz, 1 H), 2.90-2.82 (m, 1 H), 2.73-2.67 (m, 1 H).

**[0224] (S)-(5-methylisochroman-1-yl)methanamine (72):** (ESI) m/z: 178 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, MeOD-*d*<sub>4</sub>)  $\delta$  7.19-7.13 (m, 2 H), 7.04-7.02 (m, 1 H), 4.28-4.23 (m, 1 H), 3.90-3.84 (m, 1 H), 3.54-3.50 (dd,  $J$ = 3.2, 13.2 Hz, 1 H), 3.22-3.16 (dd,  $J$ = 9.2, 13.2 Hz, 1 H), 2.90-2.82 (m, 1 H), 2.73-2.67 (m, 1 H).

## 2. General procedure B

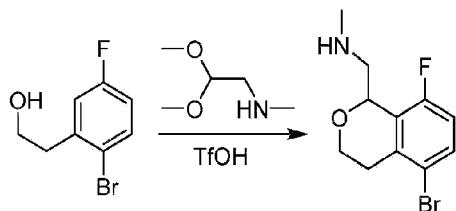
### 2.1 Preparation of (S)-1-(8-fluoroisochroman-1-yl)-N-methylmethanamine (25) and (R)-1-(8-fluoroisochroman-1-yl)-N-methylmethanamine (26)

**[0225]**



**(a). 1-(5-bromo-8-fluoroisochroman-1-yl)-N-methylmethanamine**

**[0226]**

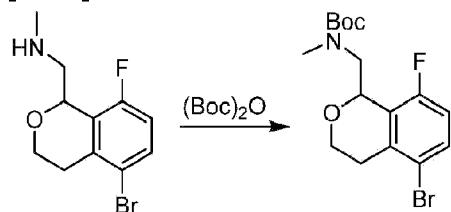


**[0227]** To a solution of 2-(2-bromo-4-fluorophenyl) ethanol (8 g, 36.5 mmol) in DCM (10 mL) was added 2, 2-dimethoxy-N-methylethanamine (6.51 g, 54.7 mmol) and trifluoromethanesulfonic acid (32.7 g, 218 mmol) at 0 °C. The reaction was stirred at ambient temperature for 16 h. Upon completion, water was added to quench the reaction and sodium hydroxide (1N, aq.) was added until pH 10-11. The resulting solution was used for next step

without further purification.

**(b). *tert*-butyl (5-bromo-8-fluoroisochroman-1-yl) methyl (methyl) carbamate**

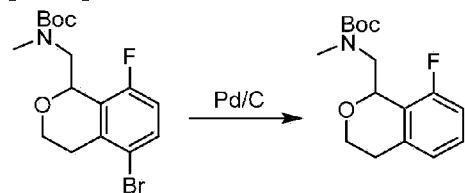
[0228]



[0229] To a solution of 1-(5-bromo-8-fluoroisochroman-1-yl)-N-methylmethanamine (8 g, 29.1 mmol) in water (150 mL) was added di-*tert*-butyl dicarbonate (9.50 g, 43.6 mmol). The reaction was stirred at ambient temperature for 3 h. Upon completion, the mixture was extracted with DCM (100mL×2). The organic layers were dried and concentrated to give the crude which was purified by silica gel chromatography (eluted from PE to PE: EA=20:1) to give the desired compound (9.26 g) as a colorless oil.

**(c). *tert*-butyl (8-fluoroisochroman-1-yl) methyl (methyl) carbamate**

[0230]

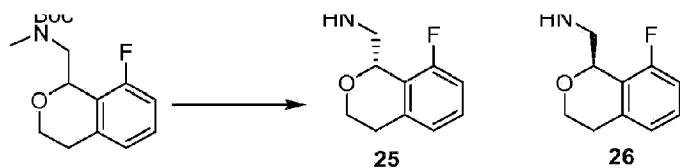


[0231] To a solution of *tert*-butyl ((5-bromo-8-fluoroisochroman-1-yl) methyl) (methyl) carbamate (9.26 g, 24.7 mmol) in methanol (100 mL) was added Pd/C (2.59 g, 24.7 mmol). The reaction was stirred at ambient temperature for 4 h under H<sub>2</sub> atmosphere. Upon completion, the mixture was filtered and concentrated. The crude was dissolved in EA (100 mL), washed with water (100 mL×2), dried and concentrated to give the crude product (6.7 g), which was used for next step without further purification.

**(d). (S)-1-(8-fluoroisochroman-1-yl)-N-methylmethanamine (25) and (R)-1-(8-fluoroisochroman-1-yl)-N-methylmethanamine (26)**

[0232]





[0233] To a solution of tert-butyl ((8-fluoroisochroman-1-yl) methyl) (methyl) carbamate (6.7 g, 22.6 mmol) in EA (20 mL) was added HCl/EA (3M, 30 mL). The mixture was stirred at ambient temperature for 16 h. Upon completion, the solvent was removed and the residue was dissolved in DCM (50 mL). The solution was neutralized with sodium hydroxide (15%, aq.), washed with water (50 mL×2) and brine (50 mL), dried and concentrated to get the racemic mixture of the desired product (3.6 g) as an oil. The mixture was separated by chiral HPLC {Column: AY-H (250×4.6mm 5um) and Mobile Phase: *n*-Hexane (0.1%DEA): ethanol (0.1%DEA) =90:10} to give (*R*)-1-(8-fluoroisochroman-1-yl)-*N*-methylmethanamine (1.25 g, **26**) as an oil and (*S*)-1-(8-fluoroisochroman-1-yl)-*N*-methylmethanamine (1.01 g, **25**) as an oil.

[0234] To a solution of (S)-1-(8-fluoroisochroman-1-yl)-N-methylmethanamine (1.01 g, 25) in ethyl acetate (20 mL) was added HCl in ethyl acetate (3M, 2 mL) at 0 °C. The mixture was stirred at ambient temperature for 30 mins and solvent was removed. The residue was washed with ethyl acetate (30mL), filtered and dried to give the HCl salt of (S)-1-(8-fluoroisochroman-1-yl)-N-methylmethanamine (25).

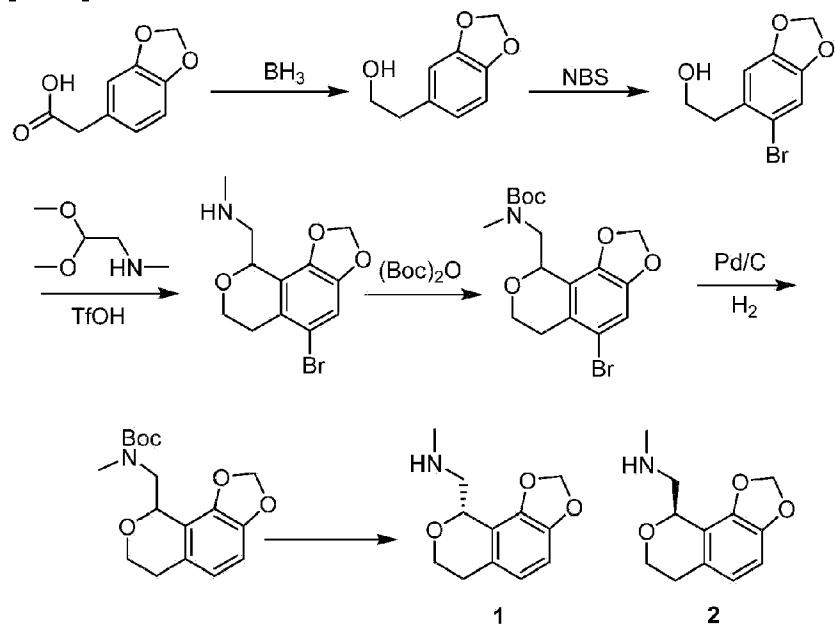
**[0235]** To a solution of (*R*)-1-(8-fluoroisochroman-1-yl)-N-methylmethanamine (1.25 g, **26**) in ethyl acetate (20 mL) was added HCl in ethyl acetate (3M, 2 mL) at 0 °C. The mixture was stirred at ambient temperature for 30 mins and solvent was removed. The residue was washed with ethyl acetate (30 mL), filtered and dried to give the HCl salt of (*R*)-1-(8-fluoroisochroman-1-yl)-N-methylmethanamine (**26**).

**[0236]** (S)-1-(8-fluoroisochroman-1-yl)-*N*-methylmethanamine (1.01 g, **25**): MS (ESI): m/z=196[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.34~7.28 (m, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.04~6.99 (m, 1H), 5.26~5.24 (m, 1H), 4.19 - 4.14 (m, 1H), 3.89~3.83 (m, 1H), 3.59-3.54 (m, 1H), 3.43~3.37(m, 1H), 2.96~2.93 (m, 1H), 2.89~2.84 (m, 1H), 2.77 (s, 3H).

**[0237]** (*R*)-1-(8-fluoroisochroman-1-yl)-*N*-methylmethanamine (1.25 g, **26**): MS (ESI): m/z=196[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.34~7.29 (m, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.04~6.99 (m, 1H), 5.26-5.24 (m, 1H), 4.19 - 4.14 (m, 1H), 3.89~3.83 (m, 1H), 3.59~3.54 (m, 1H), 3.43~3.37(m, 1H), 2.96~2.93 (m, 1H), 2.89~2.84 (m, 1H), 2.78 (s, 3H).

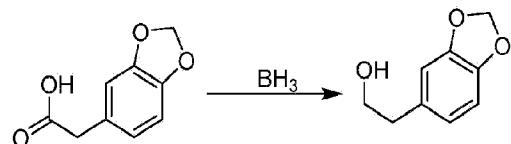
## 2.2 Preparation of (S)-1-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylmethanamine (1) and (R)-1-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylmethanamine (2) (reference examples)

[0238]



(a). 2-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol

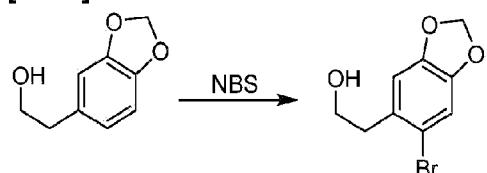
[0239]



[0240] To a solution of 2-(benzo[d][1,3]dioxol-5-yl)acetic acid (25 g, 138 mmol) in THF (100 mL) was added  $\text{BH}_3/\text{THF}$  (1 M, 160 mL) at 0 °C. The reaction was stirred at ambient temperature until complete (~16 h). Upon completion, ice water was added to quench the reaction and the mixture was extracted with EA, dried, and concentrated. The crude material (21.3 g, purity - 93%) was used for next step without further purification. MS(ESI):  $m/z$  149 [M-18+H]<sup>+</sup>

(b). 2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethan-1-ol

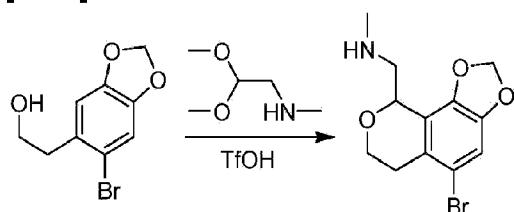
[0241]



**[0242]** To a solution of 2-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol (22 g, 132 mmol) in DCM (500 mL) was added *N*-bromosuccinimide (25.8 g, 145 mmol). The reaction was stirred at ambient temperature until complete (~3 h). Upon completion, the mixture was washed with NaHSO<sub>3</sub>, brine, dried and concentrated. The crude material (24 g, purity ~ 90%) was used for next step without further purification. MS(ESI): *m/z* 227,229 [M-18+H]<sup>+</sup>.

**(c).** *1-(5-bromo-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylmethanamine*

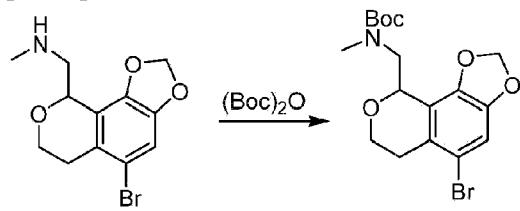
**[0243]**



**[0244]** To a solution of 2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethan-1-ol (8.76 g, 35.75 mmol) in DCM (50 mL) was added 2, 2-dimethoxy-*N*-methylethanamine (5.10 g, 42.8 mmol) and trifluoromethanesulfonic acid (26.7 g, 178 mmol) at 0 °C. The reaction was stirred at ambient temperature until complete (~16 h). Upon completion, ice water was added to quench the reaction and sodium hydroxide (1N, aq.) was added until pH 9~10. The resulting solution was extracted with DCM, dried and concentrated. The crude material (purity ~ 95%) was used for next step without further purification. MS(ESI): *m/z* 300,302 [M, M+2]<sup>+</sup>

**(d).** *tert-butyl ((5-bromo-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methyl)(methyl) carbamate*

**[0245]**

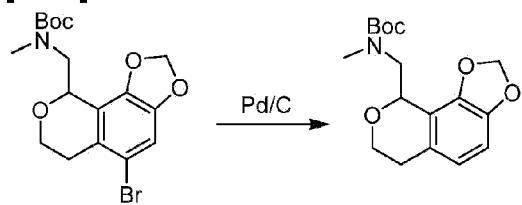


**[0246]** To a solution of 1-(5-bromo-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-*N*-methylmethanamine (9.2 g, 30.6 mmol) in DCM (100 mL) was added Et<sub>3</sub>N (3.09 g, 30.6 mmol) and di-*tert*-butyl dicarbonate (9.34 g, 42.8 mmol). The reaction was stirred at ambient temperature for 16 h. The mixture was then washed with water, dried and concentrated. The

resulting oil was purified by silica gel chromatography (eluted from PE: EA=100:0 to 85:15) to give the desired compound (12.0 g, 29.9 mmol, Yield: 98%) as a colorless oil. MS(ESI): *m/z* 300,302[M-100, M-100+2]<sup>+</sup>

(e). **tert-butyl ((6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate**

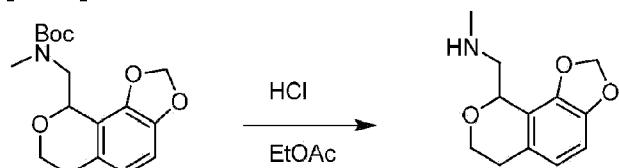
[0247]



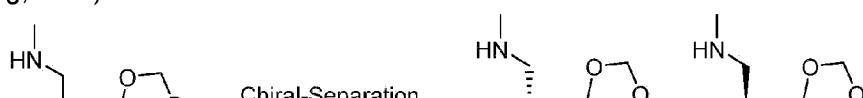
[0248] To a solution of tert-butyl ((5-bromo-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl) carbamate (12.0 g, 29.9 mmol) in methanol (100 mL) was added Pd/C (3.19 g, 29.9 mmol). The reaction was stirred at ambient temperature for 3 h under  $\text{H}_2$  atmosphere. Upon completion, the mixture was filtered and concentrated. The crude was dissolved in EA, washed with water, dried and concentrated to give the crude product, which was used for next step without further purification. MS(ESI): *m/z* 266,222[M-56+1, M-100+1]<sup>+</sup>

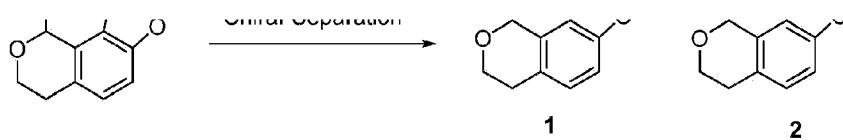
(f). **(S)-1-(6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-N-methylmethanamine (1) and (R)-1-(6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-N-methylmethanamine (2)**

[0249]



[0250] To a solution of tert-butyl ((6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate (14 g, 43.5 mmol) in EtOAc (50 mL) was added HCl/dioxane (50 mL) at 0 °C. The mixture was stirred at ambient temperature for 3 h. Upon completion, the mixture was filtered and the residue was dissolved in water, neutralized with  $\text{NH}_4\text{OH}$  (50 mL) and extracted with EtOAc (50 mL  $\times$  2), the combined organic phase was washed with brine (100 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated to dry to get the racemic mixture of the desired product (7.31 g, 76%) as a white solid.

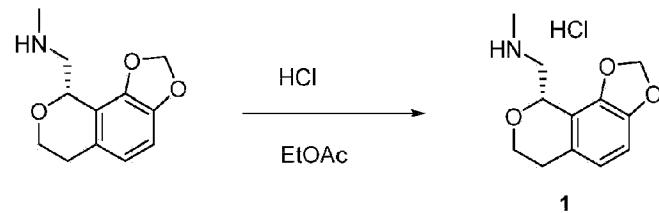




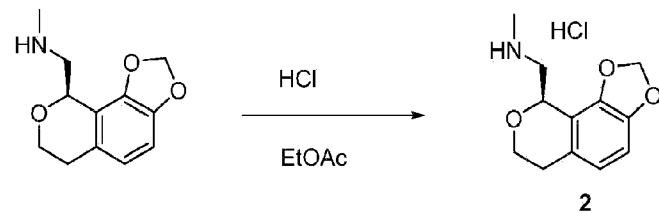
**[0251]** The racemic mixture (7.31 g) was separated by chiral HPLC {Column: Chiralpak IC (250 × 4.6 mm, 5 um) and Mobile Phase: n-Hexane (0.1%DEA): ethanol (0.1%DEA) = 80:20}.

**[0252]** (*S*)-1-(6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-*N*-methylmethanamine (**1**) (3.0 g, Yield: 41%) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.68-6.70 (d,  $J$  = 8 Hz, 1H), 6.62~6.60 (d,  $J$  = 8 Hz, 1H), 5.97 (d,  $J$  = 1.2 Hz, 1H), 5.89 (d,  $J$  = 1.6 Hz, 1H), 4.94-4.97 (dd,  $J_1$  = 8.4,  $J_2$  = 2.2 Hz, 1H), 4.06-4.11 (m, 1H), 3.72-3.78 (m, 1H), 3.15-3.19 (dd,  $J_1$  = 12.6,  $J_2$  = 2.8 Hz, 1H), 2.94~2.99 (m, 1H), 2.82~2.86 (m, 1H), 2.65~2.70 (m, 1H), 2.50 (s, 3H).

**[0253]** (*R*)-1-(6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-*N*-methylmethanamine (**2**) (3.0 g, Yield: 41%) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.69~6.71 (d,  $J$  = 7.9 Hz, 1H), 6.62~6.60 (d,  $J$  = 7.9 Hz, 1H), 5.98~6.97 (d,  $J$  = 1.4 Hz, 1H), 5.90 (d,  $J$  = 1.4 Hz, 1H), 4.95~4.98 (dd,  $J_1$  = 8.4,  $J_2$  = 2.3 Hz, 1H), 4.07~4.12 (m, 1H), 3.73~3.79 (m, 1H), 3.16~3.19 (dd,  $J_1$  = 12.6,  $J_2$  = 2.8 Hz, 1H), 2.94~3.0 (m, 1H), 2.83~2.87 (m, 1H), 2.66~2.71 (m, 1H), 2.51 (s, 3H).



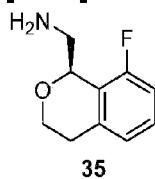
**[0254]** To a solution of (*S*)-1-(7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-*N*-methylmethanamine (**1**) (3.0 g) in EtOAc (50 mL) was added HCl/EA (4M, 5.5 mL) at 0 °C. The reaction was stirred at ambient temperature for 30 min. Upon the completion, the solvent was removed and the residue was the desired compound (**1**, 3.26 g, Yield: 93%) hydrochloride salt as a white solid. Chiral HPLC: Column Chiralpak IC (250 × 4.6 mm, 5 um; Mobile Phase: *n*-Hexane (0.1% DEA):EtOH (0.1% DEA) = 80:20; Temp = 40 °C; Flow rate = 1.0 mL/min; Ret Time = 7.17 min; Enantiopurity: 100% ee. MS(ESI):  $m/z$  222 [ $\text{M}+\text{H}$ ] $^+$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.78 (d,  $J$  = 8 Hz, 1H), 6.71 (d,  $J$  = 8 Hz, 1H), 6.01 (s, 1H), 5.96 (s, 1H), 5.10 (m, 1H), 4.18 (m, 1H), 3.82 (m, 1H), 3.67 (m, 1H), 3.41 (m, 1H), 2.88 (m, 1H), 2.76 (s, 3H), 2.74~2.68 (m, 1H).



**[0255]** To a solution of (*R*)-1-(7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-*N*-methylmethanamine (**2**) (3.0 g) in EtOAc (50 mL) was added HCl/EA (4M, 5.5 mL) at 0 °C. The reaction was stirred at ambient temperature for 30 min. Upon the completion, the solvent was removed and the residue was the desired compound (**2**, 3.26 g, Yield: 93%) hydrochloride salt as a white solid. Chiral HPLC: Column Chiralpak IC (250 × 4.6 mm, 5 um; Mobile Phase: n-Hexane (0.1% DEA):EtOH (0.1% DEA) = 80:20; Temp = 40 °C; Flow rate = 1.0 mL/min; Ret Time = 6.18 min; Enantiopurity: 100% ee. MS(ESI): *m/z* 222 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 6.78 (d, *J* = 8 Hz, 1H), 6.71 (d, *J* = 8 Hz, 1H), 6.01 (s, 1H), 5.96 (s, 1H), 5.10 (m, 1H), 4.18 (m, 1H), 3.82 (m, 1H), 3.67 (m, 1H), 3.41 (m, 1H), 2.88 (m, 1H), 2.76 (s, 3H), 2.74~2.68 (m, 1H).

### 2.3 Preparation of (R)-(8-fluoroisochroman-1-yl)methanamine (35)

〔0256〕

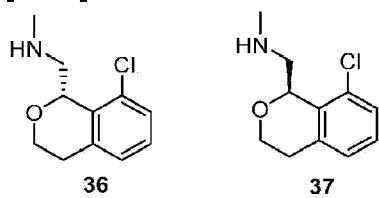


[0257] *(R)*-(8-fluoroisochroman-1-yl)methanamine (**35**) was prepared using General Procedure B and Scheme 2 starting with 2-(5-bromo-2-fluorophenyl)ethanol and 2,2-dimethoxyethanamine.

**[0258]** (R)-(8-fluoroisochroman-1-yl)methanamine (**35**): MS (ESI) m/z 182[M+H]<sup>+</sup>, <sup>1</sup>HNMR(500 MHz, CD<sub>3</sub>OD, HCl salt): 7.34~7.30 (m, 1 H), 7.09 (d, J = 8.0 Hz, 1 H), 7.04~7.00 (m, 1 H), 5.19-5.18 (m, 1H), 4.18~4.14 (m, 1 H), 3.89~3.85 (m, 1 H), 3.51 (d, J =13 Hz, 1 H), 3.33-3.27 (m, 1 H), 2.99-2.94 (m, 1 H), 2.89~2.84 (m, 1 H).

#### 2.4 Preparation of (S)-1-(8-chloroisochroman-1-yl)-N-methylmethanamine (36) and (R)-1-(8-chloroisochroman-1-yl)-N-methylmethanamine (37)

[0259]



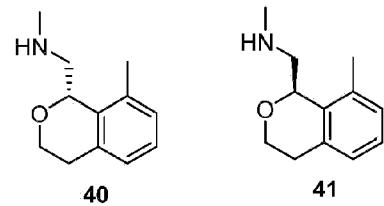
[0260] (S)-1-(8-chloroisochroman-1-yl)-N-methylmethanamine (**36**) and (R)-1-(8-chloroisochroman-1-yl)-N-methylmethanamine (**37**) were prepared using General Procedure B and Scheme 2 starting with 2-(2-bromo-5-chlorophenyl)ethanol and 2,2-dimethoxy-*N*-methylethanamine.

[0261] (S)-1-(8-chloroisochroman-1-yl)-*N*-methylmethanamine (36): MS (ESI): m/z=212[M+H]<sup>+</sup>. <sup>1</sup>HNMR(400 MHz, CD<sub>3</sub>OD, HCl salt): 7.33~7.28 (m, 2 H), 7.23 (d, *J* = 6.4 Hz, 1 H), 5.27 (dd, *J* = 2.4, 9.6 Hz, 1 H), 4.17-4.11 (m, 1 H), 3.91-3.86 (m, 1 H), 3.64 (dd, *J* = 3.2, 13.6 Hz, 1 H), 3.44 (dd, *J* = 10.0, 13.2 Hz, 1 H), 2.94~2.90 (m, 2 H), 2.80(s, 3 H).

**[0262]** (*R*)-1-(8-chloroisochroman-1-yl)-*N*-methylmethanamine (**37**): MS (ESI): m/z=212[M+H]<sup>+</sup>. <sup>1</sup>H-NMR(400 MHz, CD<sub>3</sub>OD, HCl salt): 7.34~7.28 (m, 2 H), 7.23 (d, *J* = 6.8 Hz, 1 H), 5.28 (dd, *J* = 2.8, 10.4 Hz, 1 H), 4.17~4.11 (m, 1 H), 3.91~3.86 (m, 1 H), 3.64 (dd, *J* = 2.8, 13.2 Hz, 1 H), 3.44 (dd, *J* = 10.0, 12.8 Hz, 1 H), 2.94~2.90 (m, 2 H), 2.80(s, 3 H).

## 2.5 Preparation of (S)-N-methyl-1-(8-methylisochroman-1-yl)methanamine (40) and (R)-N-methyl-1-(8-methylisochroman-1-yl)methanamine (41)

[0263]



[0264] (S)-N-methyl-1-(8-methylisochroman-1-yl)methanamine (**40**) and (R)-N-methyl-1-(8-methylisochroman-1-yl)methanamine (**41**) were prepared using General Procedure B and Scheme 2 starting with 2-(2-bromo-5-methylphenyl)ethanol and 2,2-dimethoxy-N-methylethanamine.

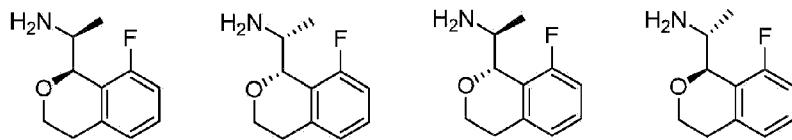
[0265] (S)-N-methyl-1-(8-methylisochroman-1-yl)methanamine (**40**): MS (ESI): m/z=192[M+H]<sup>+</sup>. <sup>1</sup>HNMR(500 MHz, CD<sub>3</sub>OD, HCl salt): 7.19~7.16 (m, 1 H), 7.10~7.04 (m, 2 H), 5.26-5.24 (m, 1 H), 4.17~4.14 (m, 1 H), 3.84~3.80 (m, 1 H), 3.38~3.35 (m, 1 H), 3.33~3.27 (m, 1 H), 2.89~2.88 (m, 2 H), 2.80(s, 3 H), 2.33(s, 3 H).

[0266] *(R)-N-methyl-1-(8-methylisochroman-1-yl)methanamine (41): MS (ESI): m/z=192[M+H]<sup>+</sup>. <sup>1</sup>HNMR(400 MHz, CD<sub>3</sub>OD, HCl salt): 7.19~7.16 (m, 1 H), 7.10~7.04 (m, 2 H), 5.26-5.25 (m, 1 H), 4.17~4.14 (m, 1 H), 3.84~3.80 (m, 1 H), 3.38~3.35 (m, 1 H), 3.33~3.27 (m, 1 H), 2.89~2.88 (m, 2 H), 2.80(s, 3 H)), 2.33(s, 3 H).*

## 2.6 Preparation of compounds (48), (49), (50), and (51): (S)-1-((R)-8-fluoroisochroman-1-

yl)ethan-1-amine, (R)-1-((S)-8-fluoroisochroman-1-yl)ethan-1-amine, (S)-1-((S)-8-fluoroisochroman-1-yl)ethan-1-amine and (R)-1-((R)-8-fluoroisochroman-1-yl)ethan-1-amine, order unknown

[0267]



[0268] ((S)-1-((R)-8-fluoroisochroman-1-yl)ethan-1-amine, (R)-1-((S)-8-fluoroisochroman-1-yl)ethan-1-amine, (S)-1-((S)-8-fluoroisochroman-1-yl)ethan-1-amine and (R)-1-((R)-8-fluoroisochroman-1-yl)ethan-1-amine were prepared using General Procedure B and Scheme 2 starting with 2-(2-bromo-5-fluorophenyl) ethanol and *tert*-butyl (1-oxopropan-2-yl)carbamate. All four stereoisomers were synthesized and characterized.

[0269] (48): MS (ESI): m/z=196 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.35~7.29 (dd, J<sub>1</sub> = 13.7, J<sub>2</sub> = 7.9 Hz, 1H), 7.10~7.08 (d, J = 7.6 Hz, 1H), 7.04~6.99 (dd, J<sub>1</sub> = 10.9, J<sub>2</sub> = 8.5 Hz, 1H), 5.25 (s, 1H), 4.31~4.27 (m, 1H), 4.09~4.00 (m, 1H), 3.74~3.68 (td, J<sub>1</sub> = 11.6, J<sub>2</sub> = 2.4 Hz, 1H), 3.11~2.98 (m, 1H), 2.75~2.71 (d, J = 16.3 Hz, 1H), 1.06~1.05 (d, J = 6.7 Hz, 3H).

[0270] (49): MS (ESI): m/z=196 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.35~7.29 (dd, J<sub>1</sub> = 13.7, J<sub>2</sub> = 7.9 Hz, 1H), 7.10~7.08 (d, J = 7.6 Hz, 1H), 7.04~6.99 (dd, J<sub>1</sub> = 10.9, J<sub>2</sub> = 8.5 Hz, 1H), 5.25 (s, 1H), 4.31~4.27 (m, 1H), 4.09~4.00 (m, 1H), 3.74~3.68 (td, J<sub>1</sub> = 11.6, J<sub>2</sub> = 2.4 Hz, 1H), 3.11~2.98 (m, 1H), 2.75~2.71 (d, J = 16.3 Hz, 1H), 1.06~1.05 (d, J = 6.7 Hz, 3H).

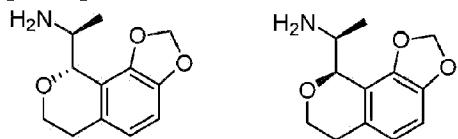
[0271] (50): MS (ESI): m/z=196 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.35~7.31(dd, J<sub>1</sub>= 13.8, J<sub>2</sub>=7.8 Hz, 1H), 7.13~7.01 (m, 2H), 5.07 (s, 1H), 4.34~4.28 (dd, J<sub>1</sub>= 11.0, J<sub>2</sub>= 5.0 Hz, 1H), 3.95~3.93 (m, 1H), 3.74~3.67 (td, J<sub>1</sub>=11.3, J<sub>2</sub>= 2.3 Hz, 1H), 3.13~3.05 (m, 1H), 2.75~2.71 (d, J = 16.3 Hz, 1H), 1.51~1.50(d, J = 6.8 Hz, 3H).

[0272] (51): MS (ESI): m/z=196 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.35~7.31(dd, J<sub>1</sub>= 13.8, J<sub>2</sub>=7.8 Hz, 1H), 7.13~7.01 (m, 2H), 5.07 (s, 1H), 4.34~4.28 (dd, J<sub>1</sub>= 11.0, J<sub>2</sub>= 5.0 Hz, 1H), 3.95~3.93 (m, 1H), 3.74~3.67 (td, J<sub>1</sub>=11.3, J<sub>2</sub>= 2.3 Hz, 1H), 3.13~3.05 (m, 1H), 2.75~2.71 (d, J = 16.3 Hz, 1H), 1.51~1.50 (d, J = 6.8 Hz, 3H).

**2.7 Preparation of compounds (55) and (54): (S)-1-((S)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)ethan-1-amine and (S)-1-((R)-6,9-dihydro-7H-[1,3]dioxolo[4,5-**

*h]isochromen-9-yl)ethan-1-amine (reference examples), order unknown*

[0273]



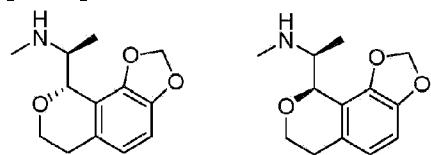
[0274] ((S)-1-((S)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)ethan-1-amine and (S)-1-((R)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)ethan-1-amine were prepared using General Procedure B and Scheme 2 starting with 2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethanol and (S)-*tert*-butyl (1-oxopropan-2-yl)carbamate. These two stereoisomers were synthesized and characterized.

[0275] (55): MS (ESI): m/z = 222 [M + H]<sup>+</sup>. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD, HCl salt):  $\delta$  6.82 (d, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 7.6 Hz, 1 H), 6.05-5.97 (m, 2 H), 4.91 (s, 1 H), 4.29-4.25 (m, 1 H), 4.17-4.13 (m, 1 H), 3.77-3.71 (m, 1 H), 3.06-2.98 (m, 1 H), 2.66 (d, *J* = 16.0 Hz, 1 H), 1.52 (d, *J* = 7.2 Hz, 3 H).

[0276] (54): MS (ESI): m/z = 222 [M + H]<sup>+</sup>. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD, HCl salt):  $\delta$  6.80-6.71 (m, 2 H), 6.01-5.94 (m, 2 H), 5.09 (s, 1 H), 4.30-4.25 (m, 1 H), 4.16 (s, 1 H), 3.77-3.71 (m, 1 H), 3.00-2.92 (m, 1 H), 2.66 (d, *J* = 15.6 Hz, 1 H), 1.12 (d, *J* = 6.8 Hz, 3 H).

**2.8 Preparation of compounds (57) and (56): (S)-1-((S)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylethan-1-amine and (S)-1-((R)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylethan-1-amine (reference examples), order unknown**

[0277]



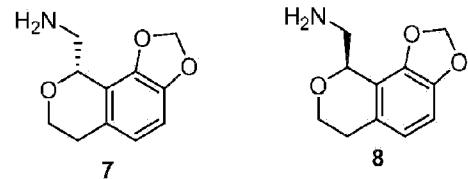
[0278] (S)-1-((S)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylethan-1-amine and (S)-1-((R)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylethan-1-amine were prepared using General Procedure B and Scheme 2 starting with 2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethanol and *tert*-butyl (S)-methyl(1-oxopropan-2-yl)carbamate. These two stereoisomers were synthesized and characterized.

**[0279] (57):** MS (ESI):  $m/z$  = 236 [M + H]<sup>+</sup>. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD, HCl salt):  $\delta$  6.84 (d,  $J$  = 8.0 Hz, 1 H), 6.76 (d,  $J$  = 8.0 Hz, 1 H), 6.06-5.97 (m, 2 H), 4.96 (s, 1 H), 4.31-4.27 (m, 1 H), 4.10-4.05 (m, 1 H), 3.79-3.73 (m, 1 H), 3.07-2.99 (m, 1 H), 2.69 (d,  $J$  = 16.0 Hz, 1 H), 2.59 (s, 3 H), 1.55 (d,  $J$  = 6.8 Hz, 3 H).

**[0280] (56):** MS (ESI):  $m/z$  = 236 [M + H]<sup>+</sup>. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD, HCl salt):  $\delta$  6.80 (d,  $J$  = 8.0 Hz, 1 H), 6.74 (d,  $J$  = 8.0 Hz, 1 H), 6.01-5.95 (m, 2 H), 5.23 (s, 1 H), 4.29-4.25 (m, 1 H), 4.03-3.97 (m, 1 H), 3.79-3.73 (m, 1 H), 3.01-2.93 (m, 1 H), 2.81 (s, 3 H), 2.67 (d,  $J$  = 16.4 Hz, 1 H), 1.14 (d,  $J$  = 6.8 Hz, 3 H).

**2.9 Preparation of (S)-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methanamine (7) and (R)-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methanamine (8) (reference examples)**

**[0281]**



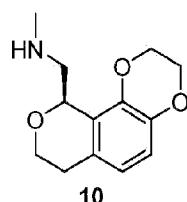
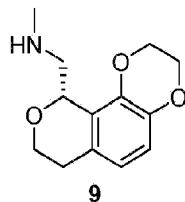
**[0282]** (S)-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methanamine (**7**) and (R)-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methanamine (**8**) were prepared using General Procedure B and Scheme 2 starting with 2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethanol and 2,2-dimethoxyethanamine.

**[0283]** (S)-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methanamine (**7**): MS (ESI):  $m/z$ =208 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt)  $\delta$  6.78 (d,  $J$  = 7.8 Hz, 1H), 6.71 (d,  $J$  = 8 Hz, 1H), 6.00 (d,  $J$  = 1.2 Hz, 1H), 5.95 (d,  $J$  = 1.2 Hz, 1H), 5.05~5.02(m, 1H), 4.19~4.14 (m, 1H), 3.84~3.78 (m, 1H), 3.61-3.56 (m, 1H), 3.31~3.26 (m, 1H), 2.95~2.87 (m, 1H), 2.73~2.67 (m, 1H).

**[0284]** (R)-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methanamine (**8**): MS (ESI):  $m/z$  = 208 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, HCl salt)  $\delta$  6.78 (d,  $J$  = 7.8 Hz, 1H), 6.71 (d,  $J$  = 8 Hz, 1H), 6.00 (d,  $J$  = 1.2 Hz, 1H), 5.95 (d,  $J$  = 1.2 Hz, 1H), 5.05~5.02(m, 1H), 4.19~4.14 (m, 1H), 3.84~3.78 (m, 1H), 3.61-3.56 (m, 1H), 3.31~3.26 (m, 1H), 2.95~2.87 (m, 1H), 2.73~2.67 (m, 1H).

**2.10 Preparation of (S)-N-methyl-1-(2,3,7,10-tetrahydro-8H-[1,4]dioxino[2,3-h]isochromen-10-yl)methanamine (**9**) and (R)-N-methyl-1-(2,3,7,10-tetrahydro-8H-[1,4]dioxino[2,3-h]isochromen-10-yl)methanamine (**10**) (reference examples)**

[0285]



[0286]

[0286] (S)-*N*-methyl-1-(2,3,7,10-tetrahydro-8*H*-[1,4]dioxino[2,3-*h*]isochromen-10-yl)methanamine (**9**) and (*R*)-*N*-methyl-1-(2,3,7,10-tetrahydro-8*H*-[1,4]dioxino[2,3-*h*]isochromen-10-yl)methanamine (**10**) were prepared using General Procedure B and Scheme 2 starting with 2-(7-bromo-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanol and 1,3-dimethoxy-*N*-methylpropan-2-amine.

〔0287〕

**[0287]** (S)-*N*-methyl-1-(2,3,7,10-tetrahydro-8*H*-[1,4]dioxino[2,3-*h*]isochromen-10-yl)methanamine (**9**): MS (ESI):  $m/z$ =236 ( $M+H$ )<sup>+</sup>. <sup>1</sup>HNMR (500 MHz, CD<sub>3</sub>OD, HCl salt):  $\delta$  6.78-6.80(d,  $J$ =9.0 Hz, 1 H), 6.69-6.71 (d,  $J$ =8.5 Hz, 1 H), 4.93-5.11 (m, 1 H), 4.34-4.39 (m, 1 H), 4.22-4.29(m,3 H),4.06-4.11 (m, 1 H), 3.78-3.82 (m, 1 H), 3.61-3.64 (m, 1H), 3.32-3.38 (m, 1 H), 2.71-2.83 (m, 5 H).

[0288]

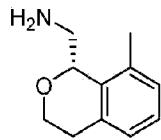
**[0288]** *(R)-Nmethyl-1-(2,3,7,10-tetrahydro-8*H*-[1,4]dioxino[2,3-*h*]isochromen-10-yl)methanamine (10):* MS (ESI):  $m/z = 236$   $[M + H]^+$ .  $^1\text{H}$ NMR (500 MHz,  $\text{CD}_3\text{OD}$ , HCl salt):  $\delta$  6.79-6.80 (d,  $J=8.9$  Hz, 1 H), 6.69-6.71 (d,  $J=8.5$  Hz, 1 H), 4.93-5.13 (m, 1 H), 4.34-4.39 (m, 1 H), 4.21-4.29 (m, 3 H), 4.06-4.11 (m, 1 H), 3.78-3.82 (m, 1 H), 3.61-3.64 (m, 1 H), 3.32-3.38 (m, 1 H), 2.71-2.84 (m, 5 H).

## 2.11 Preparation of (R)-(8-methylisochroman-1-yl)methanamine (75) and (S)-(8-methylisochroman-1-yl)methanamine (74)

[0289]



75



74

[0290] (R)-(8-methylisochroman-1-yl)methanamine (**75**) and (S)-(8-methylisochroman-1-yl)-methanamine (**74**) were prepared using General Procedure B and Scheme 2 starting with 2-(2-bromo-5-methylphenyl)ethanol and 1,3-dimethoxy-*N*-methyl- propan-2-amine.

**[0291]** (R)-(8-methylisochroman-1-yl)methanamine (**75**): MS (ESI): m/z=178 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  7.18 (t, *J* = 14.8 Hz, 1H), 7.07 (dd, *J*<sub>1</sub> = 7.2 Hz, *J*<sub>2</sub> = 7.2 Hz, 2 H), 5.18-5.15 (m, 1 H), 4.16-4.10 (m, 1 H), 3.86-3.80 (m, 1 H), 3.28-3.21 (m, 1H), 3.18-3.15 (m, 1 H), 2.90-2.87 (m, 2 H), 2.31 (s, 3 H).

**[0292]** (S)-(8-methylisochroman-1-yl)- methanamine (**74**): MS (ESI): m/z = 178 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, methanol-d<sub>4</sub>):  $\delta$  7.18 (t, *J* = 14.8 Hz, 1H), 7.07 (dd, *J*<sub>1</sub> = 7.2 Hz, *J*<sub>2</sub> = 7.2 Hz, 2 H), 5.18-5.15 (m, 1 H), 4.16-4.10 (m, 1 H), 3.86-3.80 (m, 1 H), 3.28-3.21 (m, 1H), 3.18-3.15 (m, 1 H), 2.90-2.87 (m, 2H), 2.31 (s, 3 H).

## 2.12 Preparation of (R)-(8-chloroisochroman-1-yl)methanamine (71) and (S)-(8-chloroisochroman-1-yl)methanamine (70)

[0293]



71



70

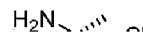
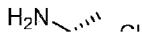
[0294] *(R)*-(8-chloroisochroman-1-yl)methanamine (**71**) and *(S)*-(8-chloroisochroman-1-yl)methanamine (**70**) were prepared using General Procedure B and Scheme 2 starting with 2-(2-bromo-5-chlorophenyl)ethanol and 1,3-dimethoxy-*N*-methyl- propan-2-amine.

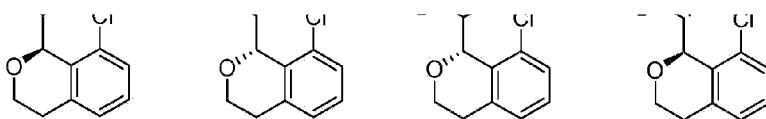
**[0295] (R)-(8-chloroisochroman-1-yl)methanamine (71):** MS (ESI):  $m/z=198$  ( $M+H$ )<sup>+</sup>.  $^1H$  NMR (400 MHz, methanol- $d_4$ ):  $\delta$  7.33-7.27 (m, 2 H), 7.23-7.21 (m, 1 H), 5.22-5.18 (m, 1 H), 4.16-4.10 (m, 1 H), 3.93-3.87 (m, 1 H), 3.61-3.56 (m, 1 H), 3.31-3.28 (m, 1 H), 2.95-2.87 (m, 2 H).

**[0296]** (S)-(8-chloroisochroman-1-yl)- methanamine (**70**): MS (ESI):  $m/z = 198$   $[M + H]^+$ .  $^1H$  NMR (400 MHz, methanol-*d*4):  $\delta$  7.33-7.27 (m, 2 H), 7.23-7.21 (m, 1 H), 5.22-5.18 (m, 1 H), 4.16-4.10 (m, 1 H), 3.93-3.87 (m, 1 H), 3.60-3.57 (m, 1 H), 3.32-3.28 (m, 1 H), 2.98-2.87 (m, 2 H).

2.13 Preparation of compounds (88) (89), (90), and (91): (S)-1-((R)-8-chloroisochroman-1-yl)ethan-1-amine, (R)-1-((S)-8-chloroisochroman-1-yl)ethan-1-amine, (S)-1-((S)-8-chloroisochroman-1-yl)ethan-1-amine and (R)-1-((R)-8-chloroisochroman-1-yl)-ethan-1-amine, order unknown

[0297]





**[0298]** ((S)-1-((R)-8-chloroisochroman-1-yl)ethan-1-amine, (R)-1-((S)-8-chloroisochroman-1-yl)ethan-1-amine, (S)-1-((S)-8-chloroisochroman-1-yl)ethan-1-amine and (R)-1-((R)-8-chloroisochroman-1-yl)ethan-1-amine were prepared using General Procedure B and Scheme 2 starting with 2-(2-bromo-5-chlorophenyl)ethanol and *t*-butyl (1-oxopropan-2-yl)carbamate.

**[0299] (88):** MS(ESI)  $m/z = 212$  [M+1]<sup>+</sup>.  $^1\text{H}$  NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  7.37-7.23 (m, 3 H), 5.33 (s, 1 H), 4.30-4.25 (m, 2 H), 3.63 (t,  $J = 26.2$  Hz, 1 H), 3.05 (t,  $J = 26.4$  Hz, 1 H), 2.73 (d,  $J = 16$  Hz, 1 H), 1.00 (d,  $J = 6.4$  Hz, 3 H).

**[0300] (89):** MS (ESI)  $m/z = 212$  [M + H]<sup>+</sup>.  $^1\text{H}$  NMR (400 MHz, methanol-*d*<sub>4</sub>)  $\delta$  7.37-7.23 (m, 3 H), 5.33 (s, 1 H), 4.30-4.25 (m, 2 H), 3.63 (t,  $J = 26.2$  Hz, 1 H), 3.05 (t,  $J = 26.4$  Hz, 1 H), 2.73 (d,  $J = 16$  Hz, 1 H), 1.00 (d,  $J = 6.4$  Hz, 3 H).

**[0301] (90):** MS(ESI)  $m/z = 212$  [M+H]<sup>+</sup>.

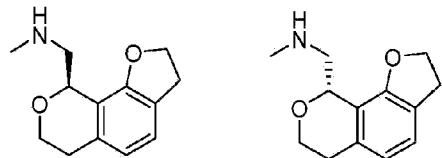
$^1\text{H}$  NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  7.38 (d,  $J = 8$  Hz, 1 H), 7.32 (t,  $J = 15.2$  Hz, 1 H), 7.24 (d,  $J = 7.6$  Hz, 1 H), 5.12 (s, 1 H), 4.30-4.26 (m, 1 H), 4.09-4.07 (m, 1 H), 3.63 (t,  $J = 24.8$  Hz, 1 H), 3.34-3.08 (m, 1 H), 2.72 (d,  $J = 16.4$  Hz, 1 H), 1.51 (d,  $J = 6.8$  Hz, 3 H).

**[0302] (91):** MS(ESI)  $m/z = 212$  [M+H]<sup>+</sup>.

$^1\text{H}$  NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  7.38 (d,  $J = 8$  Hz, 1 H), 7.32 (t,  $J = 15.2$  Hz, 1 H), 7.24 (d,  $J = 7.6$  Hz, 1 H), 5.12 (s, 1 H), 4.30-4.26 (m, 1 H), 4.09-4.07 (m, 1 H), 3.63 (t,  $J = 24.8$  Hz, 1 H), 3.34-3.08 (m, 1 H), 2.72 (d,  $J = 16.4$  Hz, 1 H), 1.51 (d,  $J = 6.8$  Hz, 3 H).

**2.14 Preparation of compounds (105) and (106): (R)-*N*-methyl-1-(2,3,6,9-tetrahydro-7H-furo[3,2-*h*]isochromen-9-yl)methanamine and (S)-*N*-methyl-1-(2,3,6,9-tetrahydro-7H-furo[3,2-*h*]isochromen-9-yl)methanamine (reference examples)**

**[0303]**

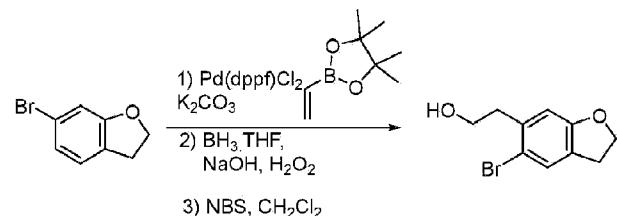


(105), (106)

**[0304]** (*R*)-*N*-methyl-1-(2,3,6,9-tetrahydro-7*H*-furo[3,2-*h*]isochromen-9-yl)methanamine and (*S*)-*N*-methyl-1-(2,3,6,9-tetrahydro-7*H*-furo[3,2-*h*]isochromen-9-yl)methanamine were prepared using General Procedure B and Scheme 2 starting with 2-(5-bromo-2,3-dihydrobenzofuran-6-yl)ethan-1-ol and 2,2-dimethoxy-*N*-methylethan-1-amine.

**(a). 2-(5-bromo-2,3-dihydrobenzofuran-6-yl)ethan-1-ol**

**[0305]**



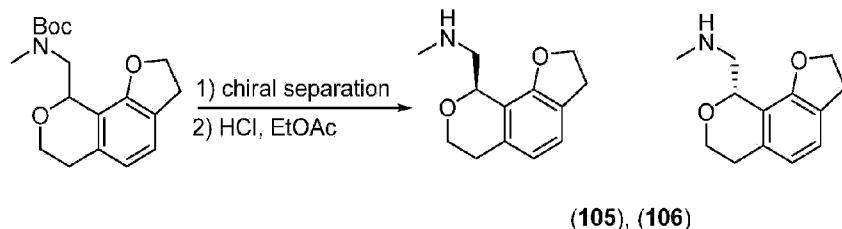
**[0306]** To a solution of 6-bromo-2,3-dihydrobenzofuran (3.8 g, 19.0 mmol) in 1,4-dioxane/H<sub>2</sub>O (100 mL/25 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (5.85 g, 38.0 mmol), K<sub>2</sub>CO<sub>3</sub> (5.24 g, 38.0 mmol) and Pd(dppf)Cl<sub>2</sub> (2.77 g, 3.80 mmol). The reaction mixture was heated to 105 °C and stirred at that temperature until the reaction was complete (~16 h). The reaction was concentrated, diluted with water and EtOAc. The combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified via silica chromatography, eluting with petroleum ether:EtOAc =20:1 to afford 6-vinyl-2,3-dihydrobenzofuran as brown oil, 2.6 g, yield=79.4%.

**[0307]** To a solution of 6-vinyl-2,3-dihydrobenzofuran (2.5 g, 17.1 mmol) in THF (20 mL) was added BH<sub>3</sub> THF (17.1 mL, 1.0 M, 17.1 mmol) at ambient temperature. The reaction was stirred at ambient temperature for 3 h, then quenched with the addition of water. A solution of sodium hydroxide in water was added followed by the addition of H<sub>2</sub>O<sub>2</sub>. The mixture was exothermic and then stirred at room temperature for 2 hours. The mixture was extracted with EtOAc, and the separated organic layer was washed with 1N FeSO<sub>4</sub> solution and brine, dried over sodium sulfate, filtered and concentrated, then purified by chromatography to give 2-(2,3-dihydrobenzofuran-6-yl)ethan-1-ol as a white solid. MS (ESI): *m/z* 165 [M + H]<sup>+</sup>.

**[0308]** To a solution of 2-(2,3-dihydrobenzofuran-6-yl)ethanol (2.2 g, 13.3 mmol) in DCM (30 mL) was added NBS (2.58 g, 14.6 mmol). The reaction was stirred at ambient temperature until complete (~2 h). Upon the completion, the mixture was washed with Na<sub>2</sub>SO<sub>3</sub> solution, brine and then dried. The residue was purified via silica chromatography, eluting with petroleum ether: EtOAc=5:1 to afford 2-(5-bromo-2,3-dihydrobenzofuran-6-yl)ethan-1-ol as white solid, 2.8 g, yield=87%. MS (ESI): *m/z* 225,227 [M-18]<sup>+</sup>.

**(b). Chiral separation, deprotection and salt formation (106)**

[0309]



[0310] *tert*-butyl methyl((3,6,7,9-tetrahydro-2*H*-furo[3,2-*h*]isochromen-9-yl)methyl) carbamate (1.4 g, 4.38 mmol) was separated into its enantiomers (*R*)-*tert*-butyl methyl((3,6,7,9-tetrahydro-2*H*-furo[3,2-*h*]isochromen-9-yl)methyl)carbamate and (*R*)-*tert*-butylmethyl((3,6,7,9-tetrahydro-2*H*-furo[3,2-*h*]isochromen-9-yl)methyl)carbamate by SFC-200 (Thar, Waters) using AD 20 × 250 mm, 5 um (Dacel) and mobile phase CO<sub>2</sub>/MeOH (0.2% methanol in ammonia) = 90/10, Flow rate = 140 g/min; Back pressure = 100 Bar; Cycle time of stack injections = 2.5 min.

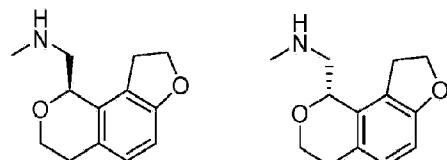
[0311] Chiral HPLC for ee determination: Column AY-H (250\*4.6 mm, 5 um; Mobile Phase: *n*-Hexane (0.1% DEA):EtOH (0.1% DEA) = 80:20; Temp = 40 °C; Flow rate = 1.0 mL/min.

[0312] Compound 105: Ret Time = 7.471 min; Enantiopurity: 99.7% ee. MS (ESI): *m/z* 220 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>): δ 7.13 (d, 1H), 6.71 (d, 1H), 5.07- 5.05 (m, 1H), 4.68- 4.54 (m, 2H), 4.18-4.13 (m, 1H), 3.85-3.79 (m, 1H), 3.70-3.67 (m, 1H), 3.39-3.32 (m, 1H), 3.21 (t, 2H), 2.96-2.89 (m, 1H), 2.75 (s, 3H), 2.76-2.72 (m, 1H).

[0313] Compound 106: Ret Time = 6.274 min; Enantiopurity: 100% ee. MS (ESI): *m/z* 220 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>): δ 7.13 (d, 1H), 6.71 (d, 1H), 5.07- 5.05 (m, 1H), 4.68- 4.54 (m, 2H), 4.18-4.13 (m, 1H), 3.85-3.79 (m, 1H), 3.70-3.67 (m, 1H), 3.39-3.32 (m, 1H), 3.21 (t, 2H), 2.96-2.89 (m, 1H), 2.75 (s, 3H), 2.76-2.72 (m, 1H).

**2.15 Preparation of compounds (107) and (108): (*R*)-*N*-methyl-1-(3,4,8,9-tetrahydro-1*H*-furo[2,3-*h*] isochromen-1-yl)methanamine and (*S*)-*N*-methyl-1-(3,4,8,9-tetrahydro-1*H*-furo[2,3-*h*]isochromen-1-yl)methanamine (reference examples)**

[0314]

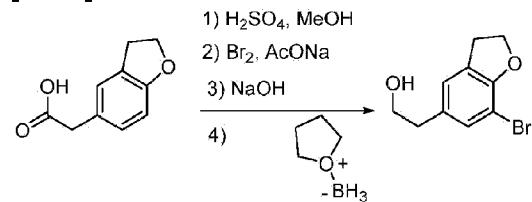


(107), (108)

**[0315]** (*R*)-*N*-methyl-1-(3,4,8,9-tetrahydro-1*H*-furo[2,3-*h*]isochromen-1-yl)methanamine and (*S*)-*N*-methyl-1-(3,4,8,9-tetrahydro-1*H*-furo[2,3-*h*]isochromen-1-yl)methanamine were prepared using General Procedure B and Scheme 2 starting with 2-(7-bromo-2,3-dihydrobenzofuran-5-yl)ethan-1-ol and 2,2-dimethoxy-*N*-methylethan-1-amine.

**(a). 2-(7-bromo-2,3-dihydrobenzofuran-5-yl)ethan-1-ol**

**[0316]**



**[0317]** To a solution of 2-(2,3-dihydrobenzofuran-5-yl)acetic acid (4 g, 22.4 mmol) in methanol (40 mL) was added sulfuric acid (219 mg, 2.24 mmol). The reaction mixture was heated to 70 °C and stirred at that temperature for 2 h. The mixture was concentrated and the residue was added ethyl acetate (50 mL). The solution was washed with brine, then the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide methyl 2-(2,3-dihydrobenzofuran-5-yl)acetate (4.0 g, yield: 93%) as a yellow oil. MS(ESI): *m/z* 193 [M+H]<sup>+</sup>.

**[0318]** To a solution of methyl 2-(2,3-dihydrobenzofuran-5-yl)acetate (4 g, 20.8 mmol) in  $\text{AcOH}$  (40 mL) was added sodium acetate (1.70 g, 20.8 mmol) and bromine (4.31 g, 27.0 mmol) at 0 °C. The reaction was stirred at ambient temperature for 2 h. Water was added, and the mixture was extracted with  $\text{EtOAc}$ . The combined organic phase was washed with brine, then dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ $\text{EtOAc}$  = 5/1) to provide methyl 2-(7-bromo-2,3-dihydrobenzofuran-5-yl) acetate (4.60 g, 16.9 mmol) as a yellow oil. MS(ESI): *m/z* 271 [M+H]<sup>+</sup>.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.17 (s, 1 H), 7.05 (s, 1 H), 4.65 (t,  $J$  = 8.8 Hz, 2 H), 3.70 (s, 3 H), 3.52 (s, 2 H), 3.30 (t,  $J$  = 8.8 Hz, 2 H).

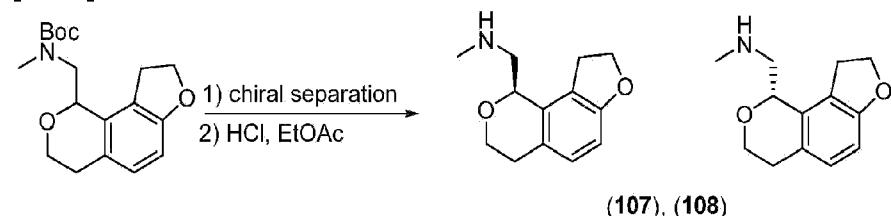
**[0319]** To a solution of methyl 2-(7-bromo-2,3-dihydrobenzofuran-5-yl)acetate (9.0 g, 33.1 mmol) in  $\text{THF}/\text{H}_2\text{O}$  (2/1) (100 mL) was added sodium hydroxide (3.97 g, 99.3 mmol). The reaction was stirred at ambient temperature for 16 h. Then the mixture was concentrated to remove THF. The residue was acidified by 2 M  $\text{HCl}$  (aq) to pH = 2. The mixture was extracted with  $\text{EtOAc}$ , and the combined organics were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to provide 2-(7-bromo-2,3-dihydrobenzofuran-5-yl)acetic acid (8.10 g,

yield: 95%) as a yellow solid. MS(ESI): *m/z* 257 [M+H]+.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.18 (s, 1 H), 7.05 (s, 1 H), 4.66 (t, *J* = 8.6 Hz, 2H), 3.53 (s, 2 H), 3.30 (t, *J* = 8.8 Hz, 2 H).

**[0320]** To a solution of 2-(7-bromo-2,3-dihydrobenzofuran-5-yl)acetic acid (4.0 g, 15.5 mmol) in THF (10 mL) was added  $\text{BH}_3$ -THF (31.0 mL, 31.0 mmol). The reaction was stirred at ambient temperature for 2 h. Water (10 mL) was added slowly to quench the reaction. The mixture was extracted with  $\text{EtOAc}$ , and the combined organics were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (petroleum ether/ $\text{EtOAc}$  = 5/1) to provide 2-(7-bromo-2,3-dihydrobenzofuran-5-yl)ethanol (3.55 g, yield: 47%) as a yellow oil. MS(ESI): *m/z* 225 [M-OH-]+.

**(b). Chiral separation, deprotection and salt formation.**

**[0321]**



**[0322]** *Tert*-butylmethyl((3,4,8,9-tetrahydro-1*H*-furo[2,3-*h*]isochromen-1-yl)methyl) carbamate (1 g, 3.13 mmol) was separated into its enantiomers by SFC-80 (Thar, Waters) using column: IC 20  $\times$  250mm, 10  $\mu\text{m}$  (Daicel) and mobile phase:  $\text{CO}_2$ /IPA(0.2% methanol in ammonia) = 80/20; Flow rate = 80 g/min; Back pressure = 100 bar.

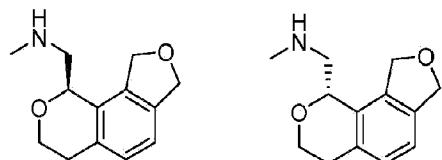
**[0323]** Chiral HPLC for ee determination: Column AY-H (250\*4.6 mm, 5  $\mu\text{m}$ ; Mobile Phase: *n*-Hexane (0.1% DEA): $\text{EtOH}$  (0.1% DEA) = 90:10; Temp = 40  $^{\circ}\text{C}$ ; Flow rate = 1.0 mL/min.

**[0324]** Compound **107** hydrochloride salt: Ret Time = 12.37 min; Enantiopurity: 100% ee. MS(ESI): *m/z* 220 [M+H]+.  $^1\text{H-NMR}$  (methanol- $d_4$ )  $\delta$  6.97 (d, *J* = 8.5 Hz, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 5.11 (dd, *J* = 2.5/9.5 Hz, 1 H), 4.67-4.64 (m, 1H), 4.52-4.47 (m, 1H), 4.17-4.13 (m, 1 H), 3.84-3.80 (m, 1 H), 3.45-3.42 (m, 1 H), 3.36-3.32 (m, 1 H), 3.25-3.20 (m, 1 H), 3.18-3.13 (m, 1 H), 2.90-2.86 (m, 1 H), 2.85 (s, 3 H), 2.85-2.73 (m, 1 H).

**[0325]** Compound **108** hydrochloride salt: Ret Time = 11.53 min; Enantiopurity: 99.7% ee. MS(ESI): *m/z* 220 [M+H]+.  $^1\text{H-NMR}$  (methanol- $d_4$ )  $\delta$  6.97 (d, *J* = 8.5 Hz, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 5.11 (dd, *J* = 2.5/9.5 Hz, 1 H), 4.67-4.64 (m, 1H), 4.52-4.47 (m, 1H), 4.17-4.13 (m, 1 H), 3.84-3.80 (m, 1 H), 3.45-3.42 (m, 1 H), 3.36-3.32 (m, 1 H), 3.25-3.20 (m, 1 H), 3.18-3.13 (m, 1 H), 2.90-2.86 (m, 1 H), 2.85 (s, 3 H), 2.85-2.73 (m, 1 H).

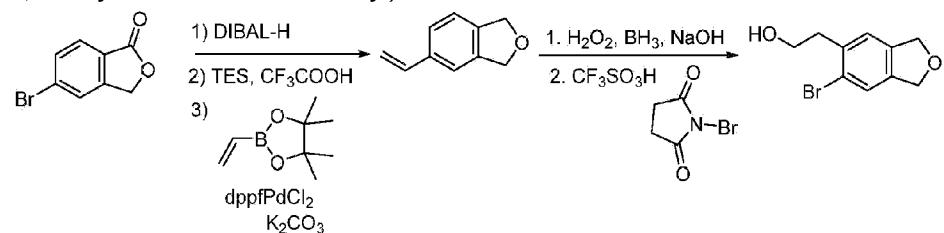
**2.16 Preparation of compounds (109) and (110): (R)-N-methyl-1-(1,6,7,9-tetrahydro-3H-furo[3,4-h]isochromen-9-yl)methanamine and (S)- N-methyl-1-(1,6,7,9-tetrahydro-3H-furo[3,4-h] isochromen-9-yl)methanamine (reference examples), order unknown**

[0326]



(109), (110)

**[0327] (R)-N-methyl-1-(1,6,7,9-tetrahydro-3H-furo[3,4-h]isochromen-9-yl)methanamine and (S)-N-methyl-1-(1,6,7,9-tetrahydro-3H-furo[3,4-h]isochromen-9-yl)methanamine were prepared using General Procedure B and Scheme 2 starting with 2-(6-bromo-1,3-dihydroisobenzofuran-5-yl)ethanol and 2,2-dimethoxy-N-methylethan-1-amine(a). 2-(6-bromo-1,3-dihydroisobenzofuran-5-yl)ethan-1-ol**



**[0328]** To a solution of 5-bromo-1,3-dihydroisobenzofuran-1(3H)-one (21.3 g, 100 mmol) in DCM (200mL) was added diisobutylaluminium hydride (184 g, 130 mmol) at -78 °C. The reaction was stirred at -78 °C until the reaction was complete (~ 2 h). 10 mL water was added, and 10mL 4M NaOH (aq.) was added, then 40mL water was added, the mixture was stirred at room temperature for 30 mins. The mixture was filtered, the filtrate was concentrated. The resulting solid was purified by flash column chromatography (petroleum ether:EtOAc 100:0 to 80:20) to provide 5-bromo-1,3-dihydroisobenzofuran-1-ol (13 g, 60.4 mol) as a white solid. MS (ESI): *m/z* 196.9 [M - 16 + 1]<sup>+</sup>.

**[0329]** To a solution of 5-bromo-1,3-dihydroisobenzofuran-1-ol (12 g, 105 mmol) in DCM (10 mL) was added triethylsilane (32 g, 278mmol) and 2,2,2-trifluoroacetic acid (12.6 g, 111mmol) at 0 °C. The reaction was stirred at ambient temperature for 12 h. The mixture was concentrated. 3M aqueous NaOH (40 mL) was added to the reaction vessel and the resulting biphasic mixture was transferred to a separatory funnel. The layers were separated and the aqueous phase was washed with EtOAc (2 × 25 mL). The combined organics were washed with saturated aqueous NaCl (2 × 50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography with a

gradient elution of EtOAc (0%) and petroleum ether (100%) to EtOAc (20%) and petroleum ether (80%) to provide 5-bromo-1,3-dihydroisobenzofuran (10.2 g, 51.2 mmol) as a white solid. MS (ESI): *m/z* 200 [M + H]<sup>+</sup>.

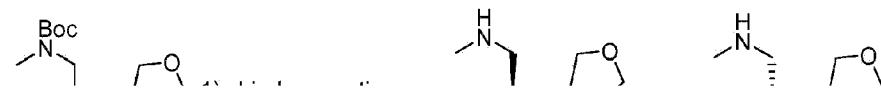
**[0330]** To a solution of 5-bromo-1,3-dihydroisobenzofuran (7.9 g, 39.6 mmol) in 1,4-dioxane/H<sub>2</sub>O (60 mL) was added K<sub>2</sub>CO<sub>3</sub> (10.9 g, 79.2 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (9.14 g, 59.4 mmol) and 1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (2.89 g, 3.96 mmol). The reaction mixture was heated to 100 °C and stirred at that temperature for 12 h. EtOAc and H<sub>2</sub>O were added. The layers were separated and the aqueous phase was washed with EtOAc. The combined organics were saturated aqueous NaCl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (petroleum ether: EtOAc 100:0 to 90: 10) to provide 5-vinyl-1,3-dihydroisobenzofuran (4.50 g, 30.7 mmol) as a colorless oil. MS(ESI): *m/z* 147 [M+H]<sup>+</sup>

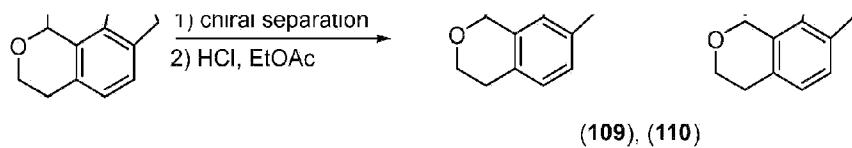
**[0331]** To a solution of 5-vinyl-1,3-dihydroisobenzofuran (1.46 g, 10 mmol) in THF (10 mL) was added BH<sub>3</sub>·THF (83 mg, 600 mmol). The reaction was stirred at room temperature for 3 h, quenched with the addition of water, then sodium hydroxide (4 g, 100 mmol) was added followed by the addition of H<sub>2</sub>O<sub>2</sub> (3.4 g, 1000 mmol). The mixture was exothermic and then stirred at room temperature for 2 hours. The mixture was washed with FeSO<sub>4</sub> solution, EtOAc (50 mL) was added, the layers were separated and the organic phase was washed with EtOAc. The combined organics were washed with saturated aqueous NaCl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (petroleum ether: EtOAc 100:0 to 80:20) to provide 2-(1,3-dihydroisobenzofuran-5-yl)ethanol (2.80 g, 17.0 mmol) as a colorless oil. MS(ESI): *m/z* 165 [M+H]<sup>+</sup>.

**[0332]** To a solution of 2-(1,3-dihydroisobenzofuran-5-yl)ethanol (656 mg, 4 mmol) in DCM (10 mL) was added 1-bromopyrrolidine-2,5-dione (711 mg, 4.00 mmol) and trifluoromethanesulfonic acid (3.00 g, 20.0 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min. Ice-water (10 mL) was added. NaOH solid was added to adjust to pH =14, then the layers were separated and the aqueous phase was washed with DCM. The combined organics were washed with saturated aqueous NaCl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (petroleum ether to EtOAc 100:0 to 80:20) to provide 2-(6-bromo-1,3-dihydroisobenzofuran-5-yl)ethanol (1.10 g, 4.52 mmol) as a colorless oil. MS(ESI): *m/z* 227 [M-17+H]<sup>+</sup>.

**(b). Chiral separation, deprotection and salt formation.**

**[0333]**





**[0334]** *tert*-butyl methyl((3,6,7,9-tetrahydro-1*H*-furo[3,4-*h*]isochromen-9-yl)methyl) carbamate (1g, 3.13 mmol) was separated into its enantiomers (*S*)-*tert*-butyl methyl((3,6,7,9-tetrahydro-1*H*-furo[3,4-*h*]isochromen-9-yl)methyl)carbamate (400 mg, 1.25 mmol) and (*R*)-*tert*-butyl methyl((3,6,7,9-tetrahydro-1*H*-furo[3,4-*h*] isochromen-9-yl)methyl) carbamate (400 mg, 1.25 mmol) by SFC-80 (Thar, Waters) using Column: IC 20 × 250 mm, 10 um (Daicel) and mobile phase: CO<sub>2</sub>/MeOH (0.2% Methanol Ammonia) = 87/13. Flow rate = 80 g/min; Back pressure = 100 bar; Cycle time of stack injections: 6.5 min.

**[0335]** Chiral HPLC for ee determination: Column AY-H (100\*4.6 mm, 5 um; Cosolvent: EtOH (0.1% methanol in ammonia); Temp = 44 °C; Flow rate = 1.0 mL/min.

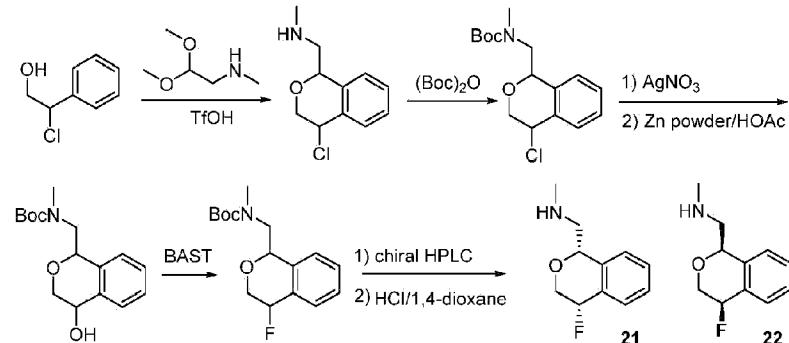
**[0336]** Compound **109** hydrochloride salt; Ret Time = 1.02 min; Enantiopurity: 100% ee. MS (ESI): *m/z* 220 [M + H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.41 (s, 1H), 8.68 (s, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 5.15 -4.96 (m, 5H), 4.08-4.02 (m, 1H), 3.83-3.78 (m, 1H), 3.33-3.26 (m, 1H), 3.10-3.04 (m, 1H), 2.84-2.82 (m, 2H), 2.59 (t, *J* = 4.8 Hz, 3H).

**[0337]** Compound **110** hydrochloride salt: Ret Time = 1.81 min; Enantiopurity: 99.2% ee. MS (ESI): *m/z* 220 [M + H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.52 (s, 1H), 8.72 (s, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 5.16 -4.96 (m, 5H), 4.08- .02 (m, 1H), 3.83-3.78 (m, 1H), 3.33-3.26 (m, 1H), 3.08-3.05 (m, 1H), 2.84-2.76 (m, 2H), 2.59 (s, 3H).

### General Procedure C

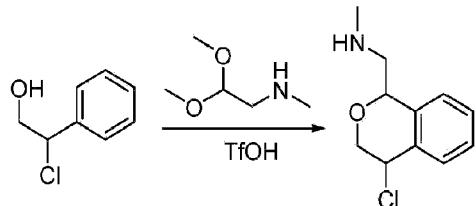
#### 3.1 Preparation of 1-((1*S*,4*S*)-4-fluoroisochroman-1-yl)-*N*-methylmethanamine (**21**) and 1-((1*R*,4*R*)-4-fluoroisochroman-1-yl)-*N*-methylmethanamine (**22**) (reference examples)

**[0338]**



**(a). 1-(4-chloroisochroman-1-yl)-N-methylmethanamine**

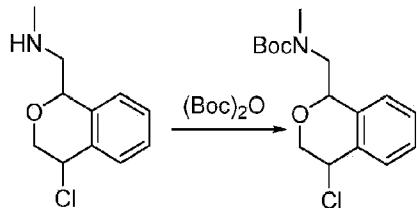
[0339]



[0340] To a solution of 2-chloro-2-phenylethanol (8 g, 33.7 mmol) and 2,2-dimethoxy-*N*-methylethanamine (9.72 g 81.6 mmol) in DCM (100 mL) was added trifluoromethanesulfonic acid (36.6 g, 244 mmol). The mixture was stirred at 15 °C for 1 day. The reaction was quenched with iced-water, and neutralized with sodium hydroxide (3N aq.) to pH=8. Then it was extracted with DCM (3×150 mL). The organic layer was separated, dried over sodium sulfate, filtered and then concentrated to give the residue. The residue was used for next step without further purification. MS (ESI): m/z=212 [M+H]<sup>+</sup>.

**(b). *tert*-butyl (4-chloroisochroman-1-yl)methyl(methyl)carbamate**

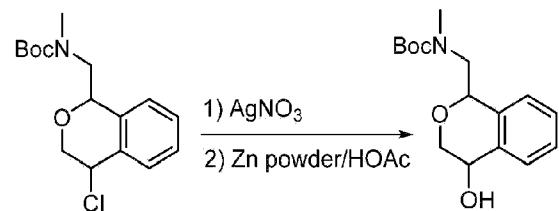
[0341]



[0342] To a solution of 1-(4-chloroisochroman-1-yl)-*N*-methylmethanamine (12 g, 31.7 mmol) in DCM (100 mL) was added sodium hydroxide (1.89 g, 47.5 mmol) and di-*tert*-butyl dicarbonate (8.29 g, 38.0 mmol). The reaction was stirred at ambient temperature for 3 h. Upon completion, the mixture was washed with water (100 mL×3). The organic layer was dried over sodium sulfate, filtered and then concentrated to give the crude product, which was purified by column chromatography (PE:EA= 80:1 to 10:1) to give *tert*-butyl ((4-chloroisochroman-1-yl)methyl)(methyl)carbamate(6.3 g).

**(c). *tert*-butyl (4-hydroxyisochroman-1-yl)methyl(methyl)carbamate**

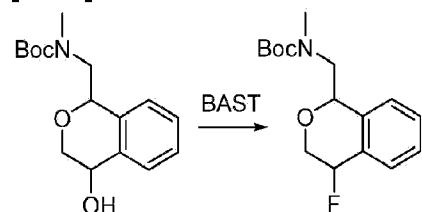
[0343]



[0344] To a solution of *tert*-butyl ((4-chloroisochroman-1-yl)methyl)(methyl)carbamate (5 g, 14.1 mmol) in THF/water (80 mL, 1:1) was added silver nitrate (11.9 g, 70.4 mmol). The mixture was stirred at 50 °C for 4h. The mixture was filtered, and the filtrate extracted by ethyl acetate (100 mL×3). The organic layer was dried over sodium sulfate and concentrated. The residue was dissolved in acetic acid (30 mL) and to it was added zinc (4.31 g, 66.0 mmol). The mixture was stirred at ambient temperature for 16 h. The mixture was diluted with ethyl acetate (200 mL), washed with water (150 mL×4). The organic layer was dried over sodium sulfate, filtered and concentrated to give the crude product, which was purified by column chromatography (PE:EA=4:1 to 1:1) to give *tert*-butyl ((4-hydroxyisochroman-1-yl)methyl)(methyl)carbamate (2.9 g).

**(d). *tert*-butyl (4-fluoroisochroman-1-yl)methyl(methyl)carbamate**

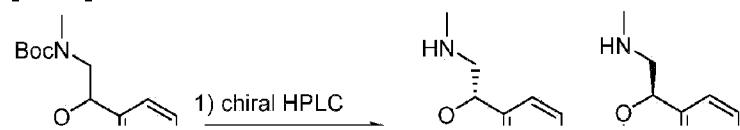
[0345]

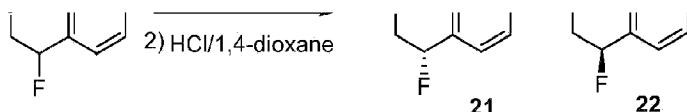


[0346] A solution of *tert*-butyl ((4-hydroxyisochroman-1-yl)methyl)(methyl)carbamate (3 g, 10.2 mmol) in BAST (9 mL) was stirred at 70 °C for 3 h. Upon completion, it was poured into iced water, extracted with ethyl acetate, The organic layer was dried over sodium sulfate, filtered and concentrated to give a residue, which was purified/separated by HPLC to give *tert*-butyl ((4-fluoroisochroman-1-yl)methyl)(methyl)carbamate (4 g) as yellow oil.

**(e). 1-((1*S*,4*S*)-4fluoroisochroman-1-yl)-*N*-methylmethanamine (21) and 1-((1*R*,4*R*)-4-fluoroisochroman-1-yl)-*N*-methylmethanamine (22)**

[0347]





**[0348]** *tert*-butyl ((4-fluoroisochroman-1-yl)methyl)(methyl)carbamate (900 mg, 3.04 mmol) was separated by chiral HPLC: {Gilson-281, column: AY-H 20×250mm, Sum (Dacel), mobile phase: Hexane(0.1%DEA)/ Ethanol(0.1%DEA)=95/5, flow rate: 50 mL/min and Cycle time: 15min} to give *tert*-butyl (((1*S*,4*S*)-4-fluoroisochroman -1-yl)methyl)(methyl)carbamate as yellow oil (300 mg) and *tert*-butyl (((1*R*,4*R*)-4-fluoroisochroman-1-yl) methyl)(methyl)carbamate as yellow oil (300 mg).

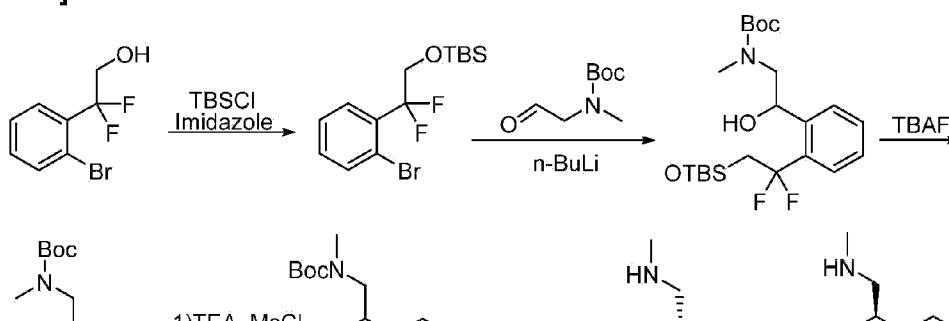
**[0349]** 1-((1*S*,4*S*)-4-fluoroisochroman-1-yl)-*N*-methylmethanamine (**21**): To a solution of *tert*-butyl (((1*S*,4*S*)-4-fluoroisochroman-1-yl)methyl) (methyl)carbamate (300 mg, 1.01 mmol) in ethyl acetate (20 mL) was added HCl/1,4-dioxane (36.3 mg, 1.01 mmol). The reaction was stirred at ambient temperature for 16 h. Upon completion, the mixture was concentrated to give (**21**) as yellow solid (0.15 g). MS (ESI): m/z=196 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.56 (d, J = 7.3 Hz, 1H), 7.50 - 7.41 (m, 2H), 7.31 (d, J = 7.2 Hz, 1H), 5.57-5.45 (m, 1H), 5.22-5.21 (m, 1H), 4.35-4.27(m, 1H), 4.09-4.03 (m, 1H), 3.50-3.43 (m, 2H), 2.82 (s, 3H).

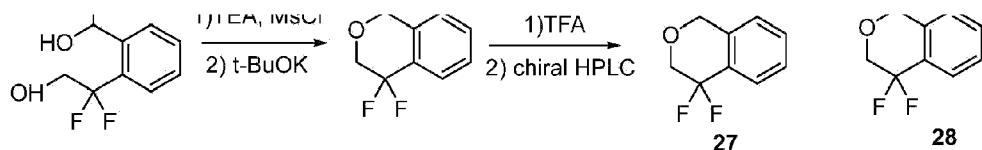
**[0350]** 1-((1*R*,4*R*)-4-fluoroisochroman-1-yl)-*N*-methylmethanamine (**22**): To a solution of *tert*-butyl (((1*R*,4*R*)-4-fluoroisochroman-1-yl) methyl) (methyl)carbamate (300 mg, 1.01 mmol) in ethyl acetate (20 mL) was added HCl/1,4-dioxane (181 mg, 5.05 mmol). The reaction was stirred at ambient temperature for 6 h. Upon completion, the mixture was concentrated to give (**22**) as yellow solid (0.16 g). MS (ESI): m/z=196 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, HCl salt) δ 7.56-7.54 (d, J = 7.5 Hz, 1H), 7.48-7.42 (m, 2H), 7.31 (d, J = 7 Hz, 1H), 5.51 (m, 1H), 5.22 (s, 1H), 4.35-4.27 (m 1H), 4.09-4.03 (m, 1H), 3.50-3.43(m, 2H), 2.82 (s, 3H).

#### General Procedure D

#### 4.1 Preparation of (*S*)-1-(4,4-difluoroisochroman-1-yl)-*N*-methylmethanamine (**27**) and (*R*)-1-(4,4-difluoroisochroman-1-yl)-*N*-methylmethanamine (**28**) (reference examples)

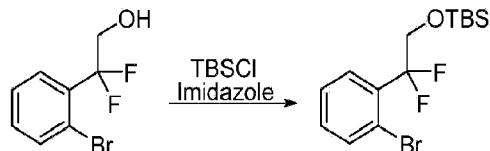
**[0351]**





**(a). (2-(2-bromophenyl)-2,2-difluoroethoxy)(tert-butyl)dimethyl silane**

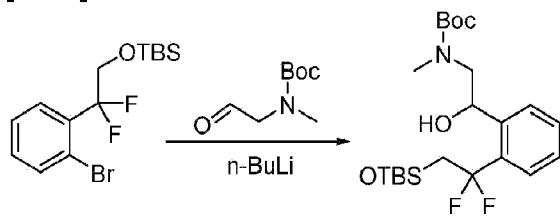
[0352]



[0353] To a solution of 2-(2-bromophenyl)-2,2-difluoroethanol (30 g, 126.3 mmol) in dichloromethane (200 mL) was added 1*H*-imidazole (17.2 g, 252.6 mmol) and *tert*-butylchlorodimethylsilane (28.5 g, 189.3 mmol). The reaction was stirred at ambient temperature for 12 h. water (200 mL) was added to the reaction vessel and the resulting biphasic mixture was transferred to a separatory funnel and extracted with dichloromethane (500 mL×2). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. The resulting oil was purified by flash column chromatography with an isocratic elution of ethyl acetate (10 %) and petroleum ether (90 %) to provide (2-(2-bromophenyl)-2,2-difluoroethoxy) (*tert*-butyl)dimethyl silane (35 g) as a colorless oil.

**(b) *tert*-butyl 2-((2-(3-(*tert*-butyldimethylsilyloxy)propyl)-5-fluorophenyl) (hydroxy)-methyl)pyrrolidine-1-carboxylate**

[0354]

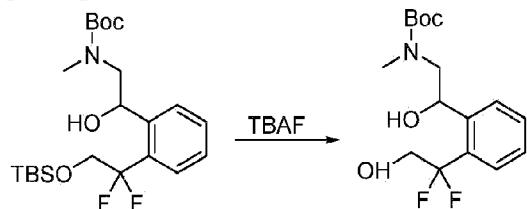


[0355] To a solution of (2-(2-bromophenyl)-2,2-difluoroethoxy)(*tert*-butyl)dimethylsilane (3.5 g, 9.96 mmol) in THF(40 mL) was added *n*-butyllithium (14.9 mmol, 2.5 N, 6 mL) at -78 °C under nitrogen. The mixture was stirred at this temperature for 2 h, then a solution of *tert*-butyl methyl(2-oxoethyl)carbamate(2.58 g, 14.9 mmol) in THF (5 mL) was added. After addition, the mixture was stirred at this temperature for 1 h, then allowed to warm to r.t. The mixture was quenched with water(100 mL), extracted with EtOAc(60 mL×2), dried and concentrated in

*vacuo* to give a residue, which was purified by silica gel chromatography eluted with PE/EtOAc = 10: 1 to provide *tert*-butyl 2-(2-(*tert*-butyldimethylsilyloxy)-1,1-difluoroethyl)phenyl)-2-hydroxyethyl(methyl)-carbamate(900 mg) as a yellow oil.

**(c). 2-(2-(1,1-difluoro-2-hydroxyethyl)phenyl)-2- hydroxyethyl(methyl)carbamate**

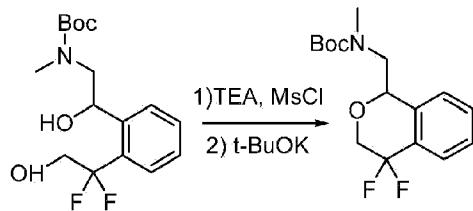
**[0356]**



**[0357]** To a solution of *tert*-butyl (2-(2-(*tert*-butyldimethylsilyloxy)-1,1-difluoroethyl)phenyl)-2-hydroxyethyl(methyl)carbamate (891 mg, 2.0 mmol) in THF (20 mL) was added TBAF (1.04 g, 4.00 mmol). The mixture was stirred at r.t. for 2 h. Upon completion, the mixture was quenched with water(100 mL), extracted with EtOAc(60 mL×2), dried and concentrated in *vacuo* to give *tert*-butyl 2-(2-(1,1-difluoro-2-hydroxyethyl)phenyl)-2-hydroxyethyl(methyl)carbamate(700 mg) as a yellow oil.

**(d). *tert*-butyl (4,4-difluoroisochroman-1-yl)methyl(methyl) carbamate**

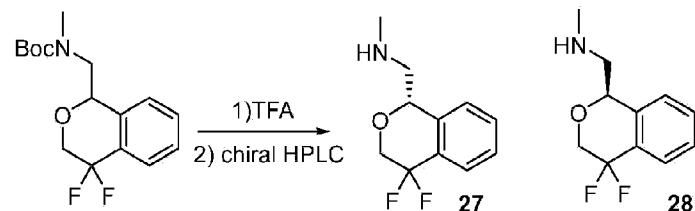
**[0358]**



**[0359]** To a solution of *tert*-butyl (2-(2-(1,1-difluoro-2-hydroxyethyl)phenyl)-2-hydroxyethyl)(methyl)carbamate (650 mg, 1.96 mmol) and TEA (808 mg, 8.0 mmol) in ethyl acetate (30 mL) was added a solution of MsCl (269 mg, 2.35 mmol) in ethyl acetate (10 mL) at 0 °C. After addition, the mixture was stirred at this temperature for 2 h. The mixture was quenched with water (30 mL), extracted with ethyl acetate (20 mL× 2), dried and concentrated in *vacuo*. The residue was dissolved in THF (20 mL) and to the solution was added *t*-BuOK (436 mg, 3.90 mmol) at 0 °C. The mixture was stirred at this temperature for 4 h. The mixture was quenched with water (100 mL), extracted with EtOAc (50 mL×2), dried and concentrated in *vacuo* to give the crude, which was purified by prep. TLC eluted with PE :EtOAc=5:1 to yield *tert*-butyl (4,4-difluoroisochroman-1-yl)methyl(methyl) carbamate(400 mg) as an oil.

(e). (S)-1-(4,4-difluoroisochroman-1-yl)-N-methylmethanamine (27) and (R)-1-(4,4-difluoroisochroman-1-yl)-N-methylmethanamine (28)

[0360]



[0361] To a solution of *tert*-butyl ((4,4-difluoroisochroman-1-yl)methyl)(methyl) carbamate (800 mg, 2.55 mmol) in DCM (15 mL) was added TFA (6 mL). The mixture was stirred at r.t. for 4 h. The mixture was evaporated in *vacuo* to remove the solvent, neutralized with 25 % aq. ammonia, extracted with DCM (30 mL × 2), dried and concentrated in *vacuo* to give 1-(4,4-difluoroisochroman-1-yl)-N- methylmethanamine (560 mg) as a yellow oil and a racemic mixture. The mixture was separated into its enantiomers (S)-1-(4,4-difluoroisochroman-1-yl)-N- methylmethanamine (27, 250 mg oil) and (R)-1-(4,4-difluoroisochroman-1-yl)-N- methylmethanamine (28, 250 mg oil) by Preparative-SFC using Instrument: SFC-80 (Thar, Waters), Column: OJ 20×250mm, Sum (Dacel), Column temperature: 35 °C and Mobile phase: CO<sub>2</sub>/ MeOH{0.5% Ammonia (7M methanal)}= 85/15. The Flow rate was 80 g/min, Back pressure was 100 bar, Detection wavelength was 240 nm and Cycle time was 3.6 min.

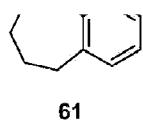
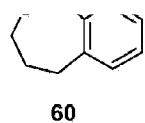
[0362] (S)-1-(4,4-difluoroisochroman-1-yl)-N -methylmethanamine (27): MS (ESI): m/z= 214[M+H]<sup>+</sup>. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): 7.75 (d, *J* = 8.0 Hz, 1 H), 7.49~7.41 (m, 2 H), 7.22 (d, *J* = 7.5 Hz, 1 H), 4.94~4.93 (m, 1 H), 4.36~4.31 (m, 1 H), 3.99~3.91 (m, 1 H), 3.14~3.11 (dd, *J* = 3.0, 12.5 Hz, 1 H), 3.03~2.99 (m, 1 H), 2.53 (s, 3H), 1.75 (brs, 1 H).

[0363] (R)-1-(4,4-difluoroisochroman-1-yl)-N-methylmethanamine (28): MS (ESI): m/z= 214[M+H]<sup>+</sup>. <sup>1</sup>H-NMR of freebase (500 MHz, CDCl<sub>3</sub>): 7.75 (d, *J* = 8.0 Hz, 1 H), 7.49~7.41 (m, 2 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 4.94~4.92 (m, 1 H), 4.36~4.30 (m, 1 H), 3.99~3.91 (m, 1 H), 3.14~3.11 (dd, *J* = 3.0, 12.5 Hz, 1 H), 3.03~2.99 (m, 1 H), 2.53 (s, 3H), 1.71 (brs, 1 H).

4.2 Preparation of (S)-1-(9-fluoro-1,3,4,5-tetrahydrobenzo[c]oxepin-1-yl)-N-methylmethanamine (60) and (R)-1-(9-fluoro-1,3,4,5-tetrahydrobenzo[c]oxepin-1-yl)-N-methylmethanamine (61) (reference examples)

[0364]



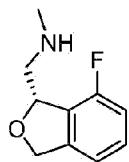
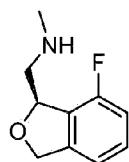


**[0365]** (S)-1-(9-fluoro-1,3,4,5-tetrahydrobenzo[c]oxepin-1-yl)-N-methylmethanamine (**60**) and (R)-1-(9-fluoro-1,3,4,5-tetrahydrobenzo[c]oxepin-1-yl)-N-methylmethanamine (**61**) were prepared using General Procedure D and Scheme 4 starting with 3-(2-bromo-3-fluorophenyl)propan-1-ol.

**[0366]** ((S)-1-(9-fluoro-1,3,4,5-tetrahydrobenzo[c]oxepin-1-yl)-N-methylmethanamine (**60**): MS (ESI):  $m/z = 210[M+H]^+$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , HCl salt): 7.33-7.28 (m, 1H), 7.07-7.00 (m, 2H), 5.35-5.33 (m, 1H), 4.19-4.13 (m, 1H), 3.74-3.67 (m, 1H), 3.52-3.46 (m, 1H), 3.40-3.33 (m, 2H), 2.79-2.72 (m, 4H), 2.17-2.11 (m, 1H), 1.83-1.76 (m, 1H). (*R*)-1-(9-fluoro-1,3,4,5-tetrahydrobenzo[c]oxepin-1-yl)-N-methylmethanamine (**61**): MS (ESI):  $m/z = 210[M+H]^+$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , HCl salt): 7.33-7.28 (m, 1H), 7.07-7.00 (m, 2H), 5.35-5.33 (m, 1H), 4.19-4.13 (m, 1H), 3.74-3.67 (m, 1H), 3.52-3.46 (m, 1H), 3.40-3.32 (m, 2H), 2.79-2.74 (m, 4H), 2.17-2.11 (m, 1H), 1.83-1.77 (m, 1H).

**4.3 Preparation of (*R*)-1-(7-fluoro-1,3-dihydroisobenzofuran-1-yl)-N-methylmethanamine (**69**) and (S)-1-(7-fluoro-1,3-dihydroisobenzofuran-1-yl)-N-methylmethanamine (**68**) (reference examples)**

**[0367]**



**[0368]** (*R*)-1-(7-fluoro-1,3-dihydroisobenzofuran-1-yl)-N-methylmethanamine (**69**) and (S)-1-(7-fluoro-1,3-dihydroisobenzofuran-1-yl)-N-methylmethanamine (**68**) were prepared using General Procedure D and Scheme 5 starting with ((2-bromo-3-fluorobenzyl)oxy)-(*tert*-butyl)dimethylsilane and 2-(benzyloxy)acetaldehyde.

**[0369]** (*R*)-1-(7-fluoro-1,3-dihydroisobenzofuran-1-yl)-N-methylmethanamine (**69**): ESI:  $m/z = 182 [M+H]^+$ .  $^1\text{H-NMR}$  (500 MHz,  $\text{MeOH-}d_4$ ):  $\delta$  7.48-7.44 (m, 1 H), 7.19 (d,  $J=7.5$  Hz, 1 H), 7.13-7.09 (m, 1 H),  $\delta$  5.69-5.67 (m, 1 H), 5.32-5.29 (dd,  $J=3$  Hz, 13 Hz, 1 H), 5.18 (d,  $J=12$  Hz, 1 H), 3.59-3.56 (dd,  $J=2.5$  Hz, 12.5 Hz, 1 H), 3.34-3.3 (m, 1 H), 2.80 (s, 3 H).

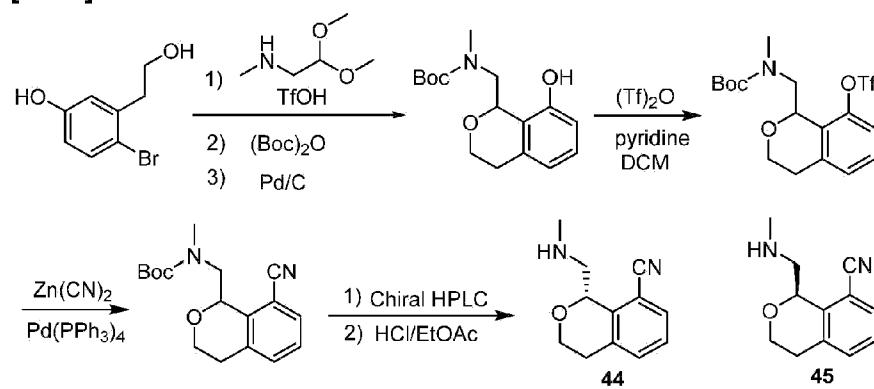
**[0370]** (S)-1-(7-fluoro-1,3-dihydroisobenzofuran-1-yl)-N-methylmethanamine (**68**): ESI:  $m/z =$

182[M+H]<sup>+</sup>. <sup>1</sup>HNMR (500 MHz, MeOH-d<sub>4</sub>): δ 7.48-7.44 (m, 1 H), 7.19 (d, J=7.5 Hz, 1 H), 7.11 (t, J=18.0 Hz, 1 H), δ 5.69-5.67(m, 1 H), 5.32-5.29(dd, J=2.5 Hz, 12.5 Hz, 1 H), 5.18 (d, J=13 Hz, 1 H), 3.59-3.56 (dd, J=3 Hz, 13 Hz, 1 H), 3.34-3.3 (m, 1 H), 2.80 (s, 3 H).

### General Procedure E

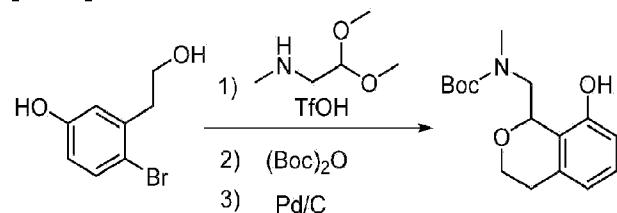
#### 5.1 Preparation of (S)-1-((methylamino)methyl)isochromane-8-carbonitrile (44) and (R)-1-((methylamino)methyl)isochromane-8-carbonitrile (45)

[0371]



#### (a). *tert*-butyl ((8-hydroxyisochroman-1-yl)methyl)(methyl)carbamate

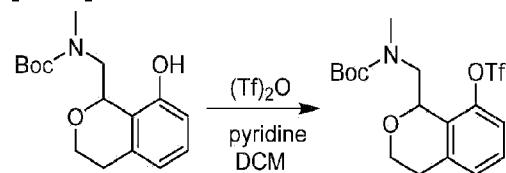
[0372]



[0373] *tert*-Butyl ((8-hydroxyisochroman-1-yl)methyl)(methyl)carbamate was prepared using General Procedure B (steps a,b,c in experimental 2.1) starting from 4-bromo-3-(2-hydroxyethyl)phenol and 2,2-dimethoxy-N-methylethan-1-amine.

#### (b). 1-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)isochroman-8-yl trifluoromethanesulfonate

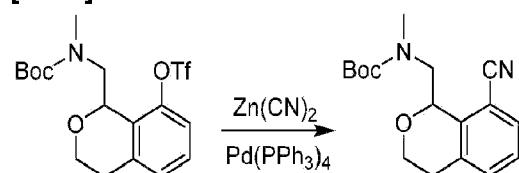
[0374]



[0375] To a solution of *tert*-butyl ((8-hydroxyisochroman-1-yl) methyl) (methyl) carbamate (1.5 g, 5.11 mmol) and pyridine (4.04 g, 51.1 mmol) in DCM (30 mL) was added trifluoromethanesulfonic anhydride (2.87 g, 10.2 mmol) at 0 °C. Upon completion, ice water (30 mL) was added to quench the reaction and the organic phase was separated and washed with HCl solution (aq. 0.12 M, 2×50 mL), dried and concentrated. The crude product was used for next step without further purification.

**(c). *tert*-butyl ((8-cyanoisochroman-1-yl)methyl)(methyl)carbamate**

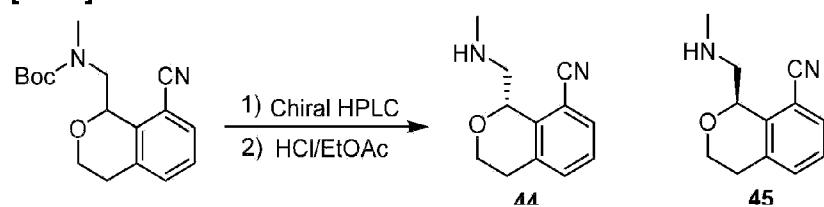
[0376]



[0377] To a solution of 1-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)isochroman-8-yl trifluoromethanesulfonate (2.17 g, 5.10 mmol) in DMSO (30 mL) was added dicyanozinc (1.19 g, 10.2 mmol) and palladium - triphenylphosphane (1:4) (588 mg, 509  $\mu\text{mol}$ ). The reaction mixture was heated to 120 °C and stirred at that temperature for 16 h. Upon completion, water was added to the mixture and then filtered and the solid was washed with EtOAc (50 mL). The combined filtrate was concentrated. The resulting oil was purified by flash column chromatography with an isocratic elution of petroleum ether (100%) and EtOAc (0%) to petroleum ether (80%) and EtOAc (20%) to provide *tert*-butyl ((8-cyanoisochroman-1-yl)methyl)(methyl)carbamate as a white solid (racemic mixture) (1.35g).

**(d). (S)-1-((methylamino)methyl)isochromane-8-carbonitrile (44) and (R)-1-((methylamino)methyl)isochromane-8-carbonitrile (45)**

[0378]



**[0379]** The racemic mixture (1.35 g) of *tert*-butyl ((8-cyanoisochroman-1-yl)methyl) (methyl)carbamate obtained above was separated by chiral HPLC: {Column: Cellulose-2 (4.6\*250mm 5um); Mobile Phase: *n*-Hexane (0.1%DEA)/ethanol (0.1%DEA) =90:10} to give (*S*)-*tert*-butyl ((8-cyanoisochroman-1-yl) methyl) (methyl) carbamate and (*R*)-*tert*-butyl ((8-cyanoisochroman-1-yl) methyl) (methyl)carbamate.

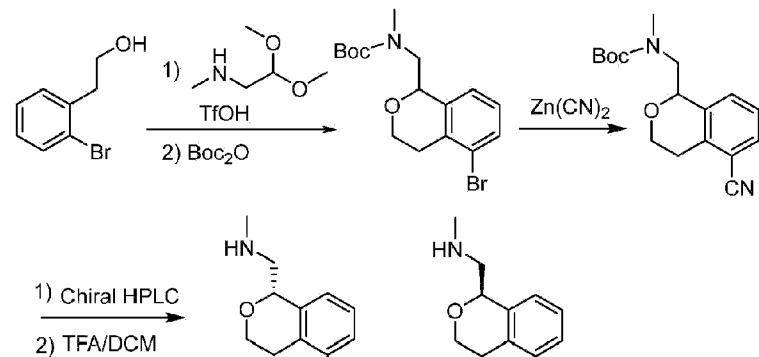
**[0380]** To a solution of (*S*)-*tert*-butyl ((8-cyanoisochroman-1-yl) methyl) (methyl) carbamate (0.45 g, 1.48 mmol) in EtOAc (20 mL) was added 3 M HCl/EtOAc (3 M, 6 mL). The reaction was stirred at ambient temperature for 16 h. Upon the completion, the solvent was removed and the residue was washed with EtOAc, filtered and dried. (*S*)-1-((methylamino)methyl)isochromane-8-carbonitrile (**44**) was obtained as a white solid (HCl salt, 281.04mg). MS (ESI): m/z=203 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.70 (d, *J* = 7.6 Hz, 1H), 7.59(d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 5.41~5.38 (dd, *J*<sub>1</sub>= 9.6, *J*<sub>2</sub>= 3.2 Hz, 1H), 4.21~4.19(m, 1H), 3.94~3.91 (m, 1H), 3.60~3.55 (m, 2H), 2.98~2.95 (m, 2H), 2.84 (s, 3H).

**[0381]** To a solution of (*R*)-*tert*-butyl ((8-cyanoisochroman-1-yl) methyl) (methyl) carbamate (0.45 g, 1.48 mmol) in EtOAc (20 mL) was added 3 M HCl/EtOAc (3M, 6mL). The reaction was stirred at ambient temperature for 16 h. Upon completion, the solvent was removed and the residue was washed with EtOAc, filtered and dried. (*R*)-1-((methylamino)methyl)isochromane-8-carbonitrile (**45**) was obtained as a white solid (HCl salt, 270.33 mg). MS (ESI): m/z=203 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.70~7.69(d, *J* = 7.6 Hz, 1H), 7.60~7.58(d, *J* = 7.8 Hz, 1H), 7.51~7.47 (t, *J* = 7.7 Hz, 1H), 5.41~5.38 (dd, *J*<sub>1</sub>= 9.8, *J*<sub>2</sub>= 2.9 Hz, 1H), 4.22~4.17(m, 1H), 3.94~3.89 (m, 1H), 3.63~3.50 (m, 2H), 2.99~2.95 (m, 2H), 2.84 (s, 3H).

#### General Procedure F

#### 6.1 Preparation of (*S*)-1-((methylamino)methyl)isochromane-5-carbonitrile (**46**) and (*R*)-1-((methylamino)methyl)isochromane-5-carbonitrile (**47**)

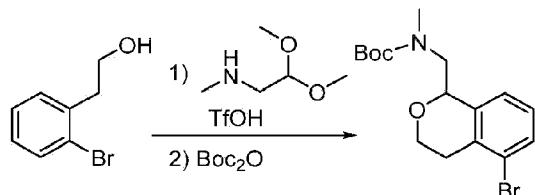
**[0382]**





**(a). *tert*-butyl ((5-bromoisochroman-1-yl)methyl)(methyl)carbamate**

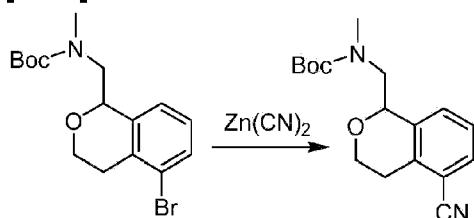
[0383]



[0384] *tert*-Butyl ((5-bromoisochroman-1-yl)methyl)(methyl)carbamate was prepared using General Procedure B (steps a,b in experimental 2.1) starting from 2-(2-bromophenyl)ethan-1-ol and 2,2-dimethoxy-N methylethan-1-amine.

**(b). *tert*-butyl ((5-cyanoisochroman-1-yl)methyl)(methyl)carbamate**

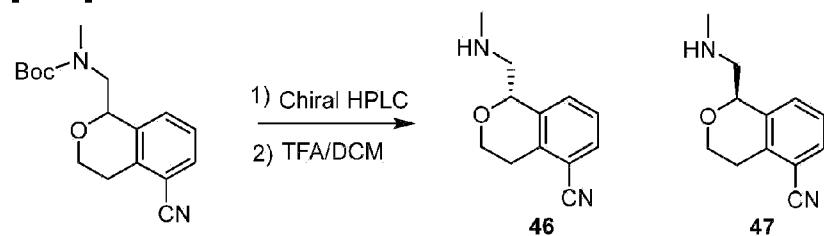
[0385]



[0386] To a solution of *tert*-butyl ((5-bromoisochroman-1-yl)methyl)(methyl)carbamate (2.0 g, 5.61 mmol) in DMSO (20 mL) was added dicyanozinc (1.31 g, 11.2 mmol) and palladium - triphenylphosphane (1:4) (648 mg, 561  $\mu$ mol). The reaction mixture was heated to 120 °C and stirred at that temperature for 16 h. Upon completion, water was added to the mixture and then filtered and the solid was washed with EtOAc (50 mL). The combined filtrate was concentrated. The resulting oil was purified by flash column chromatography with an isocratic elution of petroleum ether (100%)/EtOAc (0%) to petroleum ether (80%)/EtOAc (20%) to provide *tert*-butyl ((5-cyanoisochroman-1-yl)methyl)(methyl)carbamate as a colorless oil (racemic mixture, 1.5 g).

**(c). (S)-*tert*-butyl ((5-cyanoisochroman-1-yl)methyl)(methyl)carbamate (46) and (R)-*tert*-butyl ((5-cyanoisochroman-1-yl)methyl)(methyl)carbamate (47)**

[0387]

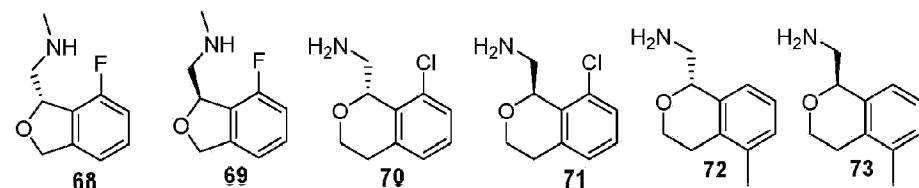


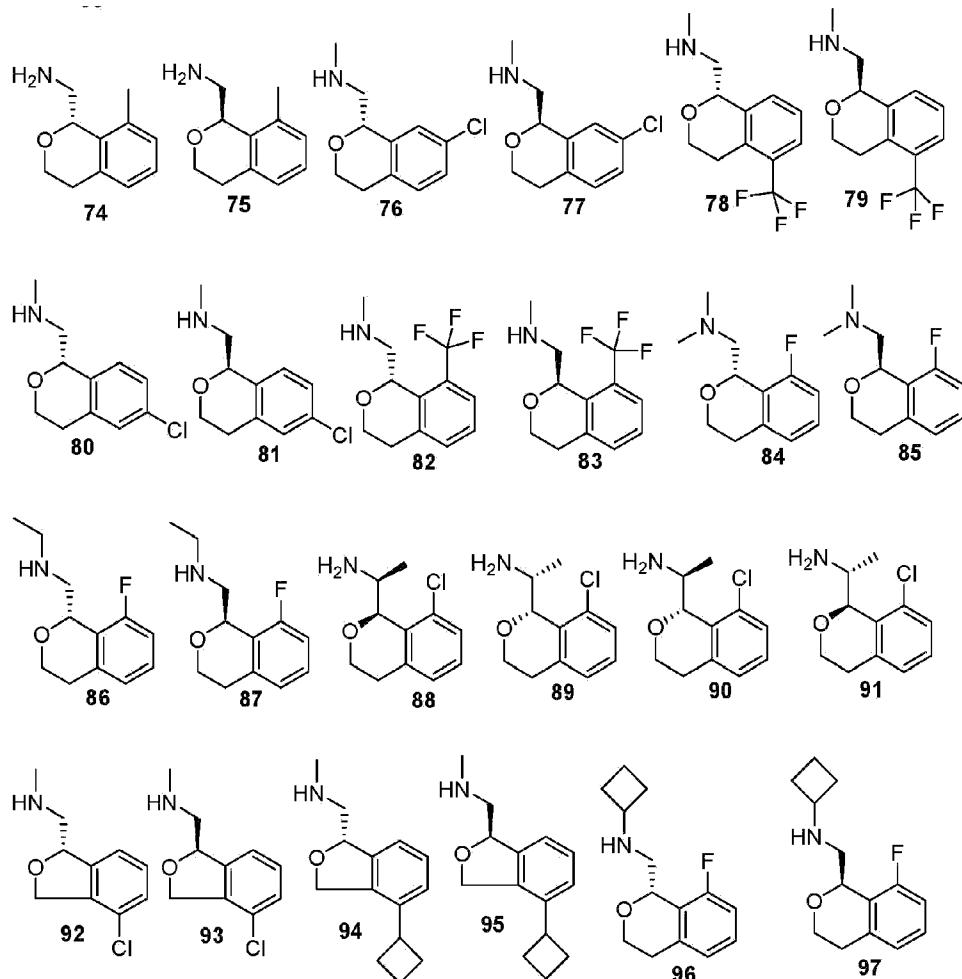
[0388] *tert*-Butyl ((5-cyanoisochroman-1-yl)methyl)(methyl)carbamate (a racemic mixture, 1.5 g) obtained above was separated into its enantiomers (*S*)-*tert*-butyl ((5-cyanoisochroman-1-yl)methyl)(methyl)carbamate and (*R*)-*tert*-butyl ((5-cyanoisochroman-1-yl)methyl)(methyl)carbamate by chiral HPLC: f preparative-SFC; co-solvent: n-Hexane(0.1%DEA)/EtOH(0.1%DEA)=90:10; column: AY-H (250\*4.6mm 5um); column temperature: 40 °C; flow rate: 10 mL/min; detection wavelength: 240 nm; cycle time: 6.7 min}.

[0389] (*S*)-*tert*-butyl (5-cyanoisochroman-1-yl)methyl(methyl)carbamate (550 mg) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at r.t. overnight and concentrated in *vacuo*. To the residue was added EtOAc (3 mL) and HCl in EtOAc (3M, 0.99 mL, 2.96 mmol). The mixture was stirred at r.t. for 15 mins. The mixture was concentrated in *vacuo* and the residue was washed with EtOAc (10 mL) to give (*S*)-1-((methylamino)methyl)isochromane-5-carbonitrile (**46**) (305 mg HCl salt) as a white solid. MS (ESI): m/z=203[M+H]<sup>+</sup>. <sup>1</sup>H NMR(400 MHz, CD<sub>3</sub>OD, HCl salt): 7.71 (d, *J* = 7.6 Hz, 1 H), 7.59~7.56 (m, 1 H), 7.49~7.44 (m, 1 H), 5.16-5.15 (m, 1 H), 4.34~4.28 (m, 1 H), 3.96~3.90 (m, 1 H), 3.67-3.65 (m, 1 H), 3.40-3.37 (m, 1 H), 3.18-3.10 (m, 1 H), 3.02~2.98 (m, 1 H), 2.80(s, 3 H).

[0390] (*R*)-*tert*-butyl (5-cyanoisochroman-1-yl)methyl(methyl)carbamate (650 mg) in DCM (2.75 mL) DCM was added TFA (1.25 mL). The mixture was stirred at r.t. overnight and concentrated in *vacuo*. To the residue was added EtOAc (3 mL) and HCl in EtOAc (3M, 1.31 mL). The mixture was stirred at r.t. for 15 mins and concentrated in *vacuo*. The residue was washed with EtOAc (10 mL) to give (*R*)-1-((methylamino)methyl)isochromane-5-carbonitrile (**47**) (401 mg HCl salt) as a white solid. MS (ESI): m/z=203[M+H]<sup>+</sup>. <sup>1</sup>H NMR(400 MHz, CD<sub>3</sub>OD): 7.71 (d, *J* = 7.6 Hz, 1 H), 7.59~7.56 (m, 1 H), 7.48~7.44 (m, 1 H), 5.16-5.14 (m, 1 H), 4.34~4.28 (m, 1 H), 3.96~3.90 (m, 1 H), 3.69-3.66 (m, 1 H), 3.40-3.37 (m, 1 H), 3.18-3.10 (m, 1 H), 3.02~2.98 (m, 1 H), 2.80(s, 3 H).

[0391] Other compounds that can be made by the methods described above include the following non-limiting examples. Compounds 68, 69, 78, 79, 82-83, 92-95 are provided for reference.

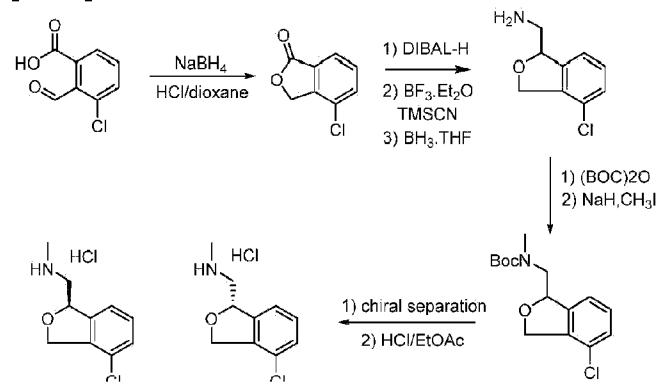




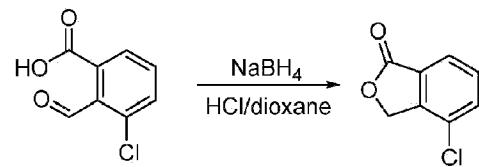
### General Procedure G

**7.1 Preparation of (R)-1-(4-chloro-1,3-dihydroisobenzofuran-1-yl)-N-methylmethanamine (93) and (S)-1-(4-chloro-1,3-dihydroisobenzofuran-1-yl)-N-methylmethanamine (92) (reference examples)**

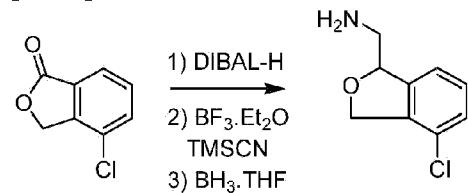
[0392]



93 92

**(a). 4-chloroisobenzofuran-1(3H)-one****[0393]**

**[0394]** To a solution of 3-chloro-2-formylbenzoic acid (24 g, 91.0 mmol) in methanol (250 mL) was added NaBH<sub>4</sub> (5.14 g, 136 mmol). The reaction was stirred at ambient temperature for 2 h. The mixture was concentrated to dryness to provide 3-chloro-2-(hydroxymethyl)benzoic acid as a yellow oil. To the oil in THF (80 mL) was added hydrogen chloride in dioxane (6N, 20 mL). The mixture was stirred at ambient temperature for 2 h and then extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (PE/EtOAc = 5/1) to provide 4-chloroisobenzofuran-1(3H)-one (12 g) as a yellow solid. MS (ESI) *m/z* = 169 [M+H]<sup>+</sup>.

**(b). (4-chloro-1,3-dihydroisobenzofuran-1-yl)methanamine****[0395]**

**[0396]** To a solution of 4-chloroisobenzofuran-1(3H)-one (7 g, 41.5 mmol) in DCM (120 mL) was cooled to -78°C, was added diisobutylaluminum hydride (7.66 g, 53.9 mmol). The mixture was stirred at -78°C for 3 h and water (2.2 mL) was added. The mixture was warmed to 0°C and 15 % NaOH (2.2 mL) and then H<sub>2</sub>O (5.4 mL) was added. The mixture was stirred at RT for 1 h and was filtered. The filtrate was dried over sodium sulfate and concentrated to provide 4-chloro-1,3-dihydroisobenzofuran-1-ol (5.00 g) as a yellow oil.

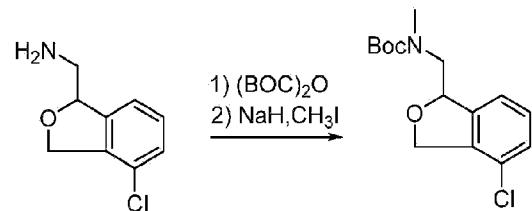
**[0397]** To a solution of 4-chloro-1,3-dihydroisobenzofuran-1-ol (5 g, 29.3 mmol) in DCM (80 mL) was added BF<sub>3</sub>·Et<sub>2</sub>O (12.4 g, 87.9 mmol) and trimethylsilanecarbonitrile (14.4 g, 146 mmol) at -20°C. The reaction was stirred at this temperature for 1 h and NaOH (60 mL, aq.

1M) was added. The resulting biphasic mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM ( $2 \times 30$  mL). The combined organics were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to provide 4-chloro-1,3-dihydroisobenzofuran-1-carbonitrile (5.00 g) as a yellow oil.

**[0398]** To a solution of 4-chloro-1,3-dihydroisobenzofuran-1-carbonitrile (5 g, 27.8 mmol) in THF (40 mL) was added  $\text{BH}_3\text{-THF}$  (7.08 g, 83.4 mmol). The reaction was stirred at ambient temperature for 3 h. Water (50 mL) was added slowly to quench the reaction. The resulting mixture was extracted with EA ( $3 \times 30$  mL). The combined organic phase was dried over sodium sulfate, filtered and the filtrate was concentrated to provide (4-chloro-1,3-dihydroisobenzofuran-1-yl)methanamine (4.00 g) as a yellow oil. MS(ESI)  $m/z = 184[\text{M}+\text{H}]^+$

**(c). *tert*-butyl ((4-chloro-1,3-dihydroisobenzofuran-1-yl)methyl)(methyl)carbamate**

**[0399]**

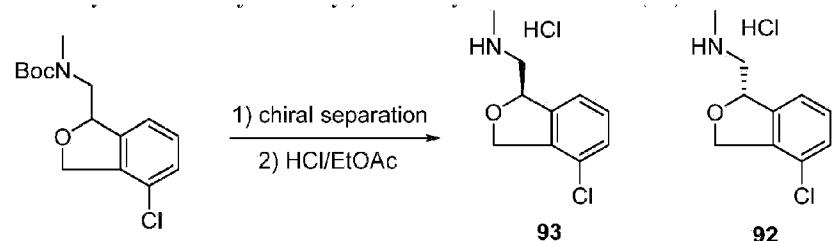


**[0400]** To a solution of (4-chloro-1,3-dihydroisobenzofuran-1-yl)methanamine (8 g, 43.5 mmol) in DCM (100 mL) was added triethylamine (13.1 g, 130 mmol) and di-*tert*-butyl dicarbonate (14.2 g, 65.2 mmol). The reaction was stirred at ambient temperature for 3 h. The mixture was then concentrated and residue purified by flash chromatography (PE/EtOAc = 10/1) to provide *tert*-butyl (4-chloro-1,3-dihydroisobenzofuran-1-yl) methyl carbamate (10.0 g) as a white solid. MS(ESI)  $m/z = 184 [\text{M}-100+\text{H}]^+$

**[0401]** To a solution of *tert*-butyl ((4-chloro-1,3-dihydroisobenzofuran-1-yl)methyl) carbamate (900 mg, 3.17 mmol) in DMF (30 mL) was added sodium hydride (152 mg, 6.34 mmol) and iodomethane (899 mg, 6.34 mmol). The reaction was stirred at ambient temperature for 1 h. water (100 mL) was added to the reaction vessel and the resulting biphasic mixture was transferred to a separatory funnel. The layers were separated and the organic phase was washed with EtOAc ( $2 \times 50$  mL) and water ( $2 \times 60$  mL). The combined organics were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography with an isocratic elution of EtOAc (10 %) and petroleum ether (90 %) to provide *tert*-butyl((4-chloro-1,3-dihydroisobenzofuran-1-yl)methyl)(methyl)carbamate (900 mg) as a colorless oil.

**(d). (*R*)-1-(4-chloro-1,3-dihydroisobenzofuran-1-yl)-*N*-methyl-methanamine (93) and (*S*)-1-(4-chloro-1,3-dihydroisobenzofuran-1-yl)-*N*-methyl-methanamine (92)**

[0402]



[0403] *tert*-Butyl ((4-chloro-1,3-dihydroisobenzofuran-1-yl)methyl)(methyl) carbamate (a racemic mixture, 900 mg) obtained above was separated into its enantiomers by chiral HPLC {solvent: MeOH (0.2% ammonia); EnantioPak AD 4.6\* 100mm 5um} to provide (*R*)-*tert*-butyl ((4-chloro-1,3-dihydroisobenzofuran-1-yl)methyl)(methyl)-

[0404] carbamate (500 mg, 100 % ee) as a colorless oil and (*S*)-*tert*-butyl ((4-chloro-1,3-dihydroisobenzofuran-1-yl)methyl)(methyl) carbamate (480 mg, 98 % ee) as a colorless oil.

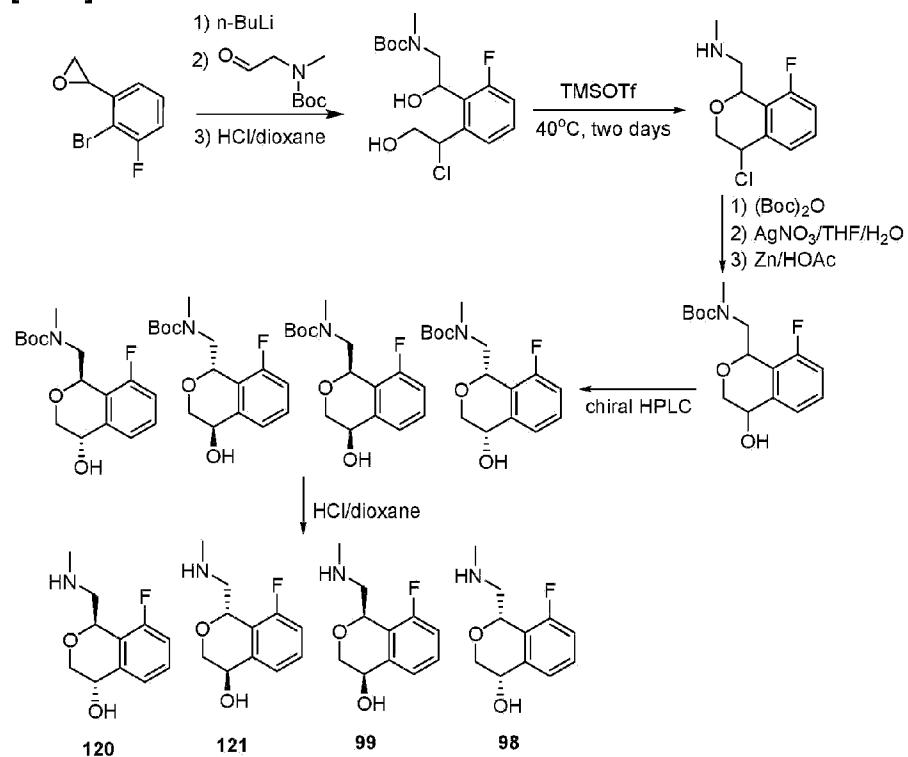
[0405] A solution of (*R*)-*tert*-butyl ((4-chloro-1,3-dihydroisobenzofuran-1-yl)methyl)(methyl) carbamate (500 mg, 1.67 mmol) in HCl/EtOAc (10 mL) was added HCl/EtOAc (10 mL, 3N). The mixture was stirred at ambient temperature for 24 h. The mixture was evaporated *in vacuo* to give the crude product as a white solid, which was washed with EtOAc to afford compound 93 hydrochloride salt as a white solid (250 mg, 100 % ee). MS (ESI): *m/z* = 198 (M+1). <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>) δ 7.41-7.39 (m, 2 H), 7.35-7.33 (m, 1 H), 5.62-5.60 (m, 1 H), 5.30-5.26 (m, 1 H) 5.19-5.15 (m, 1 H), 3.57-3.53 (m, 1 H), 3.31-3.26 (m, 1 H), 2.79 (s, 3H).

[0406] A solution of (*S*)-*tert*-butyl ((4-chloro-1,3-dihydroisobenzofuran-1-yl)methyl)(methyl) carbamate (480 mg, 1.61 mmol) in HCl/EtOAc (10 ml) was stirred at room temperature overnight. Upon completion, the mixture was evaporated *in vacuo* to give the crude product, which was washed with EtOAc to give compound 92 as a white powder hydrochloride salt (240 mg, 99 % ee). MS (ESI): *m/z* = 198 (M+1). <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>) δ 7.41-7.40 (m, 2 H), 7.34-7.33 (m, 1 H), 5.62-5.60 (m, 1 H), 5.29-5.25 (m, 1 H) 5.18-5.15 (m, 1 H), 3.57-3.53 (m, 1 H), 3.31-3.26 (m, 1 H), 2.79 (s, 3H).

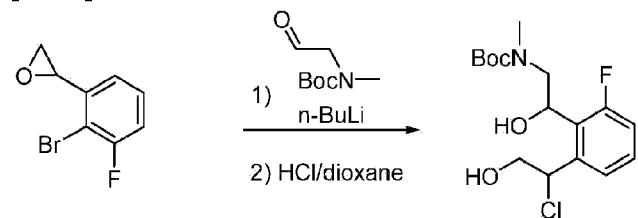
#### General Procedure H

#### 8.1 Preparation of (*1R,4R*)-8-fluoro-1-((methylamino)methyl)isochroman-4-ol (99) and (*1S,4S*)-8-fluoro-1-((methylamino)methyl)isochroman-4-ol (98)

[0407]

(a). *tert-Butyl 2-(2-fluoro-6-(oxiran-2-yl)phenyl)-2-hydroxyethyl (methyl)carbamate*

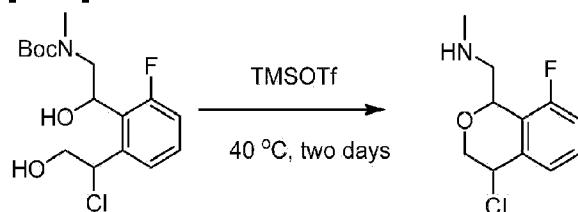
[0408]



[0409] To a solution of 2-(2-bromo-3-fluorophenyl)oxirane (11.7 g, 53.9 mmol) in tetrahydrofuran(100 mL) was added n-butyllithium(2.5 M) (24 mL, 59.2 mmol) at -78 °C. After stirring at -78 °C for 1 h, *tert*-butyl methyl(2-oxoethyl)carbamate (13.9 g, 80.8 mmol) in THF (5 mL) was added. After the mixture was stirred at this temperature for 2 h, HCl in dioxane (4M, 40 mL) was added, and the resulting mixture was warmed to RT overnight. The mixture was filtered and the filtrate was washed with water (2×50 mL), dried and concentrated. The resulting oil was purified by flash column chromatography with an isocratic elution of petroleum ether (100%) and EtOAc (0%) to petroleum ether (100%) and EtOAc (45%) to provide *tert*-butyl (2-(2-(1-chloro-2-hydroxyethyl)-6-fluoro phenyl)-2-hydroxyethyl)(methyl) carbamate(8.60 g) as a yellow oil. MS (ESI): *m/z*= 248[M+H]<sup>+</sup>.

(b). *tert-Butyl 1-(4-chloro-8-fluoroisochroman-1-yl)-N-methylmethanamine*

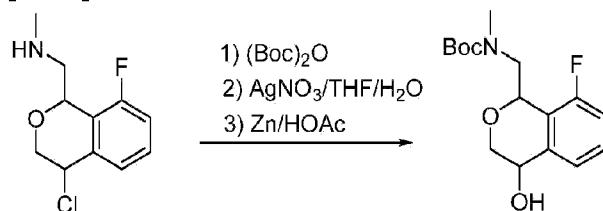
[0410]



[0411] To a solution of *tert*-butyl (2-(2-(1-chloro-2-hydroxyethyl)-6-fluorophenyl)-2-hydroxyethyl)(methyl)carbamate (0.23 g) in DCM (2 mL) was added trimethylsilyl trifluoromethanesulphonate (14.6 g, 66.1 mmol). The reaction mixture was heated to 40 °C and stirred at this temperature for 2 days. Upon completion, ice water was added to quench the reaction and NaOH (20% aqueous) solution was added to adjust pH to 10-11. The resulting mixture was used for next step without further purification. MS(ESI)  $m/z$ = 230[M+H]<sup>+</sup>

(c). *tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)methyl(methyl) carbamate

[0412]



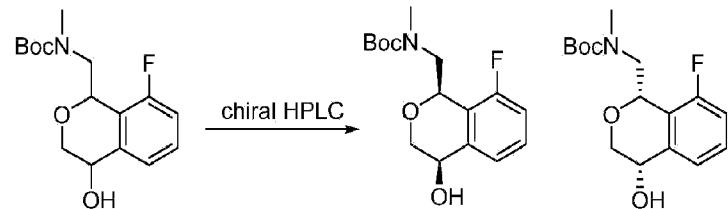
[0413] To a solution of 1-(4-chloro-8-fluoroisochroman-1-yl)-*N*-methylmethanamine (0.143 g) in water (10 mL) was added di-*tert*-butyl dicarbonate (202 mg). The reaction was stirred at ambient temperature for 3 h. Upon completion, the mixture was extracted with DCM (2×50 mL), dried and concentrated. The crude was purified by pre-TLC (PE: EtOAc =20:1) to give *tert*-butyl ((4-chloro-8-fluoroisochroman-1-yl)methyl)(methyl) carbamate (130 mg). ESI:  $m/z$ =230[M-100+H]<sup>+</sup>.

[0414] To a solution of *tert*-butyl ((4-chloro-8-fluoroisochroman-1-yl)methyl)(methyl) carbamate (130 mg) in THF/water (1:1) (30 mL) was added (nitrooxy)silver (334 mg, 1.97 mmol). The reaction mixture was stirred at ambient temperature for 30 min and then at 60 °C for 6 h. Upon completion, water (100 mL) was added to the reaction vessel and the resulting biphasic mixture was transferred to a separatory funnel. The layers were separated and the organic phase was washed with EtOAc (2×50 mL) and water (2×50 mL). The combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude oil was dissolved in HOAc (5 mL) and Zn powder was added. The mixture was stirred at RT for 6 h and water

(100 mL) was added to the reaction vessel. The resulting biphasic mixture was transferred to a separatory funnel. The layers were separated and the organic phase was washed with EtOAc (2 × 100 mL) and water (2×50 mL). The combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give an oil, which was purified by preparative HPLC to give *tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)- methyl(methyl) carbamate (3.6 g).

**(d). (1*R*,4*R*)-*tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)methyl(methyl) carbamate and (1*S*,4*S*)-*tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)methyl(methyl) carbamate**

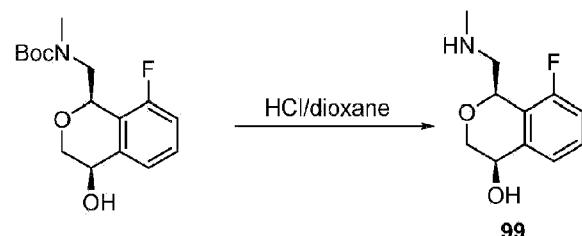
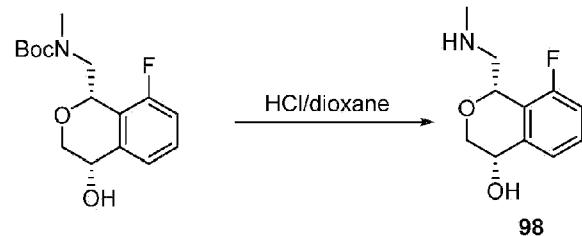
[0415]



[0416] The resulting *tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)- methyl(methyl) carbamate (3.6 g) was purified by chiral HPLC {MeOH (0.2% ammonia); AD-H (4.6\*100\*5um)} to provide the two enantiomers: (1*R*,4*R*)-*tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)methyl(methyl) carbamate (1.53 g, 100% ee) and (1*S*,4*S*)-*tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)methyl(methyl) carbamate (1.69 g, 97% ee) as a colorless oil.

**(e). (1*R*,4*R*)-8-fluoro-1-((methylamino)methyl)isochroman-4-ol (99) and (1*S*,4*S*)-8-fluoro-1-((methylamino)methyl)isochroman-4-ol (98)**

[0417]



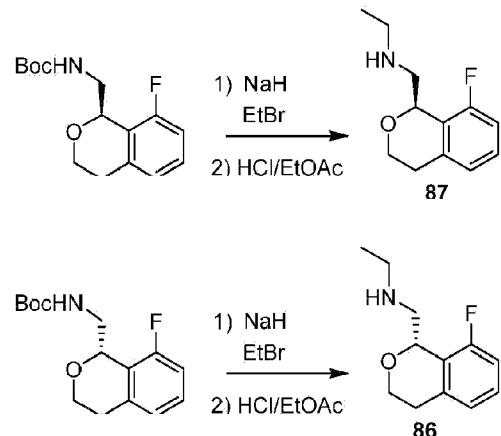
**[0418]** To a solution of (1*S*,4*S*)-*tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)methyl - (methyl) carbamate (1.69 g, 5.42 mmol) in DCM (25 mL) was added HCl in dioxane (4M, 15 mL). The mixture was stirred at ambient temperature for 3 h. Solvent was removed and the residue was dissolved in water (50 mL), the mixture was extracted with EtOAc (2×50 mL). The aqueous phase was lyophilized to give (1*S*,4*S*)-8-fluoro-1-((methylamino)methyl)isochroman-4-ol (**98**) as a white solid (1.12 g, purity: 100%, yield: 92.5%, 98% ee). ESI: *m/z*=212[M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.52(brs, 1 H), 8.83 (brs, 1 H), 7.43-7.35 (m, 2H), 7.18-7.13(m, 1 H), 5.34-5.31 (m, 1 H), 4.54(t, *J*= 4.4 Hz, 1 H), 4.10-4.06(m, 1 H), 3.61-3.57 (m, 1 H), 3.32-3.24(m, 2 H), 2.59 (t, *J*= 4.8 Hz, 3 H).

**[0419]** To a solution of (1*R*,4*R*)-*tert*-butyl (8-fluoro-4-hydroxyisochroman-1-yl)methyl - (methyl) carbamate (1.53 g, 4.91 mmol) in DCM (25 mL) was added HCl/dioxane (4M, 15 mL). The reaction was stirred at ambient temperature for 3 h. Solvent was removed and the residue was dissolved in water (50 mL) and the mixture was extracted with EtOAc (2×50 mL). The aqueous phase was lyophilized to give (1*R*,4*R*)-8-fluoro-1-((methylamino)methyl)isochroman-4-ol (**99**) as a white solid (1.16 g, purity: 100%, yield: 95.8%, 99% ee). ESI: *m/z*=212[M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.52 (brs, 1 H), 8.83 (brs, 1 H), 7.43-7.35 (m, 2H), 7.18-7.13(m, 1 H), 5.34-5.31 (m, 1 H), 4.54(t, *J*= 4.4 Hz, 1 H), 4.10-4.06(m, 1 H), 3.61-3.57 (m, 1 H), 3.32-3.24(m, 2 H), 2.59 (t, *J*= 4.8 Hz, 3 H).

### General Procedure I

#### 9.1 Preparation of (*R*)-*N*-((8-fluoroisochroman-1-yl)methyl)ethanamine (**87**) and (*S*)-*N*-((8-fluoroisochroman-1-yl)methyl)ethanamine (**86**)

##### [0420]



##### (a). (*R*)-*N*-((8-fluoroisochroman-1-yl)methyl)ethanamine (**87**)

**[0421]** To a solution of (*R*)-*tert*-butyl ((8-fluoroisochroman-1-yl)methyl)carbamate (0.5 g, 1.77 mmol) in DMF (10 mL) was added NaH (60%) (212 mg, 5.31 mmol). After stirring for 1 h, bromoethane (385 mg, 3.54 mmol) was added. The reaction was stirred at ambient temperature for 2 h. Upon the completion, EtOAc (50 mL) was added and then the mixture washed with brine (5×100 mL), dried and concentrated. The resulting oil was purified by flash column chromatography with a gradient elution of petroleum ether (100%) to petroleum ether (92%)/EtOAc (8%) to provide a colorless oil, which was dissolved in EtOAc (20 mL). To the solution was added HCl in EtOAc (3M, 6 mL). The mixture was stirred at ambient temperature for 16 h and the solvent was removed. The residue was dissolved with EtOAc (50 mL), and then filtered and dried. (*R*)-*N*-(8-fluoroisochroman-1-yl)methylethanamine (326 mg, yield: 82.9%) as a white solid was collected. (ESI) *m/z*: 210 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>) δ 7.35-7.29 (dd, *J*= 8.0, 14.0 Hz, 1 H), 7.10 (d, *J*= 7.6 Hz, 1 H), 7.04 (t, *J*= 9.4 Hz, 1 H), 5.29 (d, *J*= 8.8 Hz, 1 H), 4.21-4.15 (m, 1 H), 3.91-3.85 (m, 1 H), 3.58-3.54 (dd, *J*= 2.0, 13.2 Hz, 1 H), 3.41-3.36 (dd, *J*= 10.0, 12.8 Hz, 1 H), 3.21-3.16 (m, 2 H), 3.01-2.93 (m, 1 H), 2.90-2.83 (m, 1 H), 1.39 (m, 3 H).

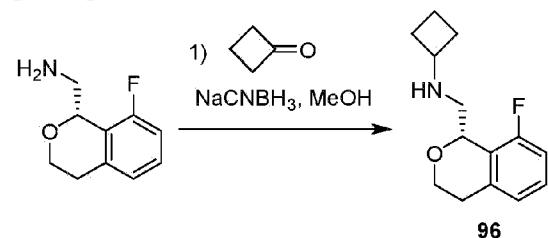
**(b). (*S*)-*N*-(8-fluoroisochroman-1-yl)methylethanamine (86)**

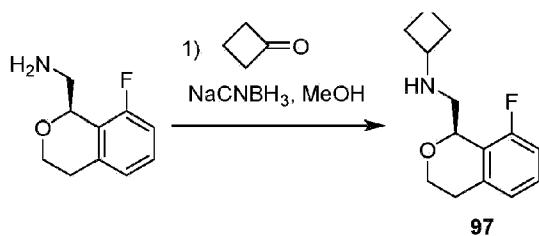
**[0422]** (*S*)-*N*-(8-fluoroisochroman-1-yl)methylethanamine (86) was prepared similarly to (*R*)-*N*-(8-fluoroisochroman-1-yl)methylethanamine (87) starting from (*S*)-*tert*-butyl ((8-fluoroisochroman-1-yl)methyl)carbamate. (ESI) *m/z*: 210 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>) δ 7.35-7.29 (dd, *J*= 8.0, 14.0 Hz, 1 H), 7.10 (d, *J*= 7.6 Hz, 1 H), 7.04 (t, *J*= 9.4 Hz, 1 H), 5.29 (d, *J*= 8.8 Hz, 1 H), 4.21-4.15 (m, 1 H), 3.91-3.85 (m, 1 H), 3.58-3.54 (dd, *J*= 2.0, 13.2 Hz, 1 H), 3.41-3.36 (dd, *J*= 10.0, 12.8 Hz, 1 H), 3.21-3.16 (m, 2 H), 3.01-2.93 (m, 1 H), 2.90-2.83 (m, 1 H), 1.39 (m, 3 H).

**General Procedure J**

**10. 1 Preparation of (*S*)-*N*-(8-fluoroisochroman-1-yl)methyl)cyclobutanamine (96) and (*S*)-*N*-(8-fluoroisochroman-1-yl)methylethanamine (97)**

**[0423]**





**(a). (S)-N-((8-fluoroisochroman-1-yl)methyl)cyclobutanamine (96)**

**[0424]** To a solution of (S)-((8-fluoroisochroman-1-yl)methyl)methanamine (0.8 g, 4.41 mmol) and cyclobutanone (401 mg, 5.73 mmol) in MeOH (30 mL) was added sodium cyanoborohydride (554 mg, 8.82 mmol). The reaction was stirred at ambient temperature for 16 h. Upon the completion, the solvent was removed and the residue was purified by pre-HPLC (0.01 % aqueous TFA) to give (S)-N-((8-fluoroisochroman-1-yl)methyl)cyclobutanamine as a yellow oil (202 mg). (ESI) *m/z*: 236 [M+H]<sup>+</sup>.

**[0425]** To a solution of (S)-N-((8-fluoroisochroman-1-yl)methyl)cyclobutanamine (0.202 g) in EtOAc (10 mL) was added HCl in EtOAc (3 M, 0.4 mL) at 0 °C. The reaction was stirred at ambient temperature for 10 mins. The solvent was removed and the residue was washed with EtOAc and PE, filtered and dried to give (S)-N-((8-fluoroisochroman-1-yl)methyl)cyclobutanamine hydrochloride salt (154 mg) as a white solid. (ESI) *m/z*: 236 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>) δ 7.35-7.29 (m, 1 H), 7.10 (d, *J*= 7.6 Hz, 1 H), 7.04-6.99 (dd, *J*= 8.8, 10.4 Hz, 1 H), 5.25-5.22 (m, 1 H), 4.20-4.14 (m, 1 H), 3.91-3.82 (m, 2 H), 3.44-3.40 (m, 1 H), 3.31-3.25 (dd, *J*= 10.0, 13.2 Hz, 1 H), 3.00-2.93 (m, 1 H), 2.90-2.83 (m, 1 H), 2.42-2.21 (m, 4 H), 1.99-1.90 (m, 2 H).

**(b). (R)-N-((8-fluoroisochroman-1-yl)methyl)cyclobutanamine (97)**

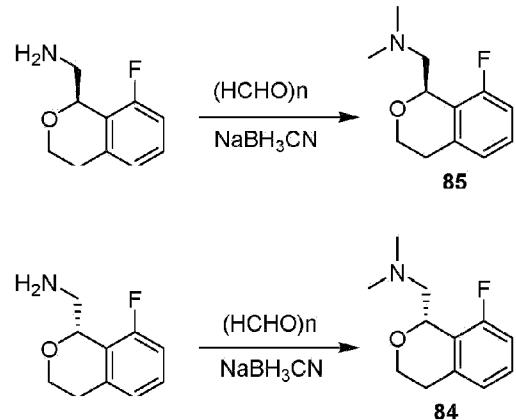
**[0426]** (R)-N-((8-fluoroisochroman-1-yl)methyl)cyclobutanamine was prepared similarly to (S)-N-((8-fluoroisochroman-1-yl)methyl)cyclobutanamine starting from (R)-N-((8-fluoroisochroman-1-yl)methyl)cyclobutanamine. (ESI) *m/z*: 236 [M+H]<sup>+</sup>.

**[0427]** <sup>1</sup>H NMR (400 MHz, methanol-*d*<sub>4</sub>) δ 7.35-7.29 (m, 1 H), 7.10 (d, *J*= 7.6 Hz, 1 H), 7.04-6.99 (dd, *J*= 8.8, 10.4 Hz, 1 H), 5.25-5.22 (m, 1 H), 4.20-4.14 (m, 1 H), 3.91-3.82 (m, 2 H), 3.44-3.40 (m, 1 H), 3.31-3.25 (dd, *J*= 10.0, 13.2 Hz, 1 H), 3.00-2.93 (m, 1 H), 2.90-2.83 (m, 1 H), 2.42-2.21 (m, 4 H), 1.99-1.90 (m, 2 H).

**General Procedure K**

**11.1 Preparation of (*R*)-1-(*S*-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine (85) and (*S*)-1-(*S*-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine (84)**

[0428]



(a). (*R*)-1-(*S*-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine (85)

[0429] To a solution of (*R*)-(8-fluoroisochroman-1-yl)methanamine (0.8 g, 4.41 mmol) in MeOH (30 mL) was added paraformaldehyde (396 mg, 13.2 mmol) and sodium cyanoborohydride (554 mg, 8.82 mmol). The reaction was stirred at ambient temperature for 3 h. Upon the completion, the solvent was removed and the residue was purified by pre-HPLC (0.01% aq. TFA) to give (*R*)-1-(8-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine as a yellow oil (402 mg), which was dissolved in EtOAc (15 mL). To the solution was added HCl in EtOAc (3M, 1 mL) and the mixture was stirred at ambient temperature for 30 mins. Solvent was removed and the residue was washed with EtOAc, filtered and dried to give (*R*)-1-(8-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine hydrochloride salt as a white solid.

[0430] (ESI)  $m/z$ : 210 [ $\text{M}+\text{H}$ ]<sup>+</sup>.  $^1\text{H-NMR}$  (400 MHz, methanol- $d_4$ )  $\delta$  7.35-7.30 (dd,  $J$ = 8.0, 14.0 Hz, 1 H), 7.11 (d,  $J$ = 7.2 Hz, 1 H), 7.05 (t,  $J$ = 9.6 Hz, 1 H), 5.44 (d,  $J$ = 9.6 Hz, 1 H), 4.23-4.17 (m, 1 H), 3.92-3.86 (m, 1 H), 3.69 (m, 1 H), 3.57 (m, 1 H), 3.07 (s, 3 H), 2.98 (m, 4 H), 2.90-2.84 (m, 1 H).

(b). (*S*)-1-(*S*-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine (84)

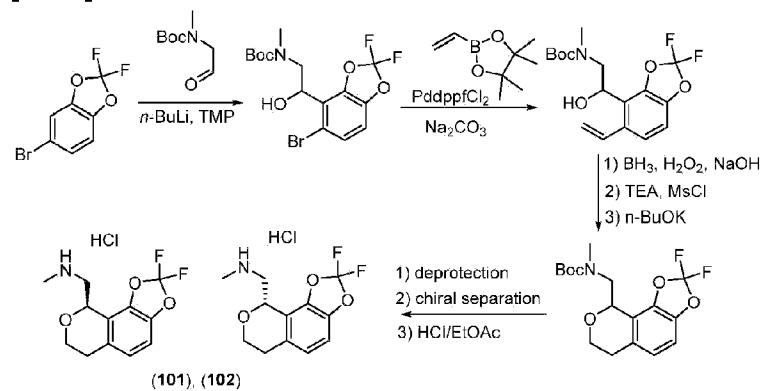
[0431] (*S*)-1-(8-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine (**84**) was synthesized similarly to (*R*)-1-(8-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine (**85**) starting from (*S*)-1-(8-fluoroisochroman-1-yl)-*N,N*-dimethylmethanamine. (ESI)  $m/z$  = 210 [ $\text{M}+\text{H}$ ]<sup>+</sup>.  $^1\text{H-NMR}$  (400 MHz, methanol- $d_4$ )  $\delta$  7.35-7.30 (dd,  $J$ = 8.0, 14.0 Hz, 1 H), 7.11 (d,  $J$ = 7.2 Hz, 1 H), 7.05 (t,  $J$ =

9.6 Hz, 1 H), 5.44 (d,  $J$  = 9.6 Hz, 1 H), 4.23-4.17 (m, 1 H), 3.92-3.86 (m, 1 H), 3.69 (m, 1 H), 3.57 (m, 1 H), 3.07 (s, 3 H), 2.98 (m, 4 H), 2.90-2.84 (m, 1 H).

### General Procedure L

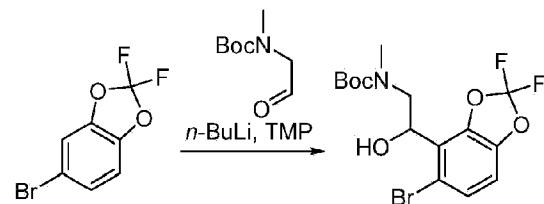
#### 12.1 Preparation of (R)-1-(2,2-difluoro-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylmethanamine (101) and (S)-1-(2,2-difluoro-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)-N-methylmethanamine (102) (reference examples), order unknown

[0432]



(a). *tert*-butyl (2-(5-bromo-2,2-difluorobenzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl)carbamate

[0433]

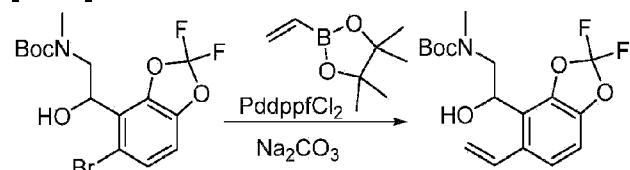


[0434] To a solution of 2,2,6,6-tetramethylpiperidine (TMP) (2.90 g, 20.6 mmol) in THF (30 mL) was added *n*-butyllithium (1.31 g, 20.6 mmol) at -78 °C. This mixture was then added to a solution of 5-bromo-2,2-difluorobenzo[d][1,3]dioxole (4.9 g, 20.6 mmol) in THF (30 mL) followed by adding *tert*-butyl (2-oxoethyl)carbamate (3.27 g, 20.6 mmol). The reaction was stirred at -78 °C until the reaction was complete (~3 h). Saturated aqueous NH<sub>4</sub>Cl was added and the resulting biphasic mixture was washed with saturated aqueous NaCl, then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (hexanes/EtOAc 90/10 to 60/40) to provide *tert*-butyl (2-(5-bromo-2,2-

difluorobenzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl)carbamate (4.46 g, 10.8 mmol) as a colorless oil.

(b). *tert-butyl (2-(2,2-difluoro-5-vinylbenzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl)carbamate*

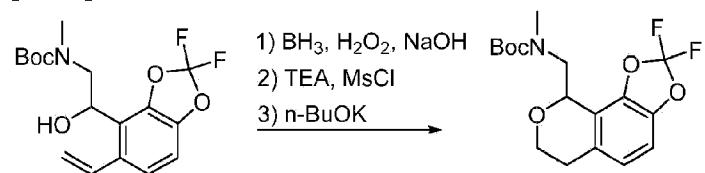
[0435]



[0436] To a solution of *tert-butyl (2-(5-bromo-2,2-difluorobenzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl)carbamate* (4.8 g, 11.7 mmol) in 1,4-dioxane (20 mL) and water (2 mL) were added  $\text{Na}_2\text{CO}_3$  (3.72 g, 35.1 mmol) and 3,3,4,4-tetramethyl-1-vinylborolane (5.26 g, 35.1 mmol). The reaction mixture was heated to 100 °C and stirred until the reaction was complete (~16 h).  $\text{EtOAc}$  was added and resulting mixture was washed with saturated aqueous  $\text{NaCl}$ . The combined organics were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Purification by flash column chromatography (hexanes/ $\text{EtOAc}$  95/5 to 70/30) provided *tert-butyl(2-(2,2-difluoro-5-vinylbenzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl) carbamate* (3.04 g, 8.50 mmol) as a yellow solid.

(c). *tert-butyl ((2,2-difluoro-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl) methyl)carbamate*

[0437]



[0438] To a solution of *tert-butyl (2-(2,2-difluoro-5-vinylbenzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl)carbamate* (2.0 g, 5.59 mmol) in THF (15 mL) was added borane (77.3 mg, 5.59 mmol). The reaction was stirred at ambient temperature for 16 h. To the reaction solution was added sodium hydroxide (22.3 mg, 559  $\mu\text{mol}$ , in 10 mL water) and hydrogen peroxide (568 mg, 16.7 mmol). The reaction was stirred at ambient temperature for 1 h, then  $\text{EtOAc}$  (250 mL) was added, then the reaction mixture was washed with saturated aqueous  $\text{NaCl}$ . The combined organics were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The resulting suspension was purified by column chromatography (hexanes/ $\text{EtOAc}$  95/5

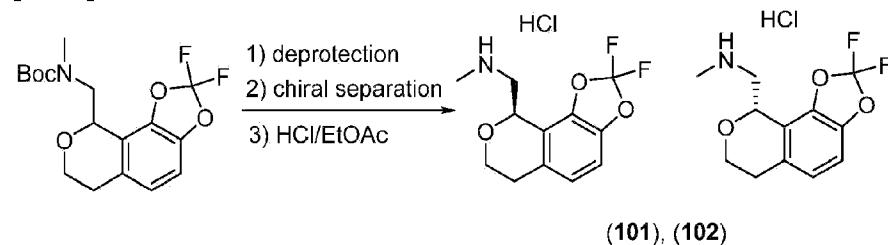
to 70/30) to provide tert-butyl (2-(2,2-difluoro-5-(2-hydroxyethyl)benzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl)carbamate (1.04 g, 2.78 mmol) as a yellow solid.

**[0439]** To a solution of tert-butyl (2-(2,2-difluoro-5-(2-hydroxyethyl)benzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl)carbamate (1.0 g, 2.66 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added methanesulfonyl chloride (334 mg, 2.92 mmol) and TEA (806 mg, 7.98 mmol). The reaction was stirred at ambient temperature until the reaction was complete (~16 h), then the reaction mixture was concentrated and purified by flash column chromatography (Hexanes/EtOAc 95/5 to 70/30) to provide 2-(4-(2-((*tert*-butoxycarbonyl)(methyl)amino)-1-hydroxyethyl)-2,2-difluorobenzo[d][1,3]dioxol-5-yl)ethyl methanesulfonate (960 mg, 2.11 mmol) as a yellow solid.

**[0440]** To a solution of 2-(4-(2-((*tert*-butoxycarbonyl)(methyl)amino)-1-hydroxyethyl)-2,2-difluorobenzo[d][1,3]dioxol-5-yl)ethyl methanesulfonate (900 mg, 1.98 mmol) in THF (5 mL) was added potassium butan-1-olate (444 mg, 3.96 mmol). The reaction was stirred at ambient temperature until the reaction was complete (~3 h), then EtOAc (200 mL) was added and the reaction mixture was washed with saturated aqueous NaCl. The combined organics were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography (Hexanes/EtOAc 90/10 to 80/20) to provide tert-butyl ((2,2-difluoro-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate (624 mg, 1.74 mmol) as a colorless oil.

**(d). Deprotection, chiral separation, and salt formation.**

**[0441]**



**[0442]** To a solution of tert-butyl (2,2-difluoro-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl(methyl)carbamate (650 mg, 2.88 mmol) in 3 M HCl/EtOAc (20 mL) was stirred at room temperature for 12 h. The mixture was concentrated *in vacuo* to get the crude, washed with EtOAc (15 mL), dried *in vacuo* to yield the desired product (468 mg, yield: 100%). MS (ESI): *m/z* 257 [M + H]<sup>+</sup>.

**[0443]** 1-(2,2-difluoro-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-*N*-methylmethanamine (468 mg) was separated into (R)-1-(2,2-difluoro-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-*N*-methylmethanamine and (S)-1-(2,2-difluoro-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)-*N*-methylmethanamine by using Column: AY-H (250 × 4.6 mm, 5  $\mu\text{m}$ ) Mobile Phase: n-Hexane (0.1% DEA):EtOH (0.1% DEA) = 90:10 Temperature: 40

°C. Inject Volume: 15  $\mu$ L.

Chiral HPLC for ee determination: Column AY-H (150\*4.6 mm, 5  $\mu$ m; Mobile Phase: n-Hexane (0.1% DEA):EtOH (0.1% DEA) = 90:10; Temp = 40 °C; Flow rate = 1.0 mL/min.

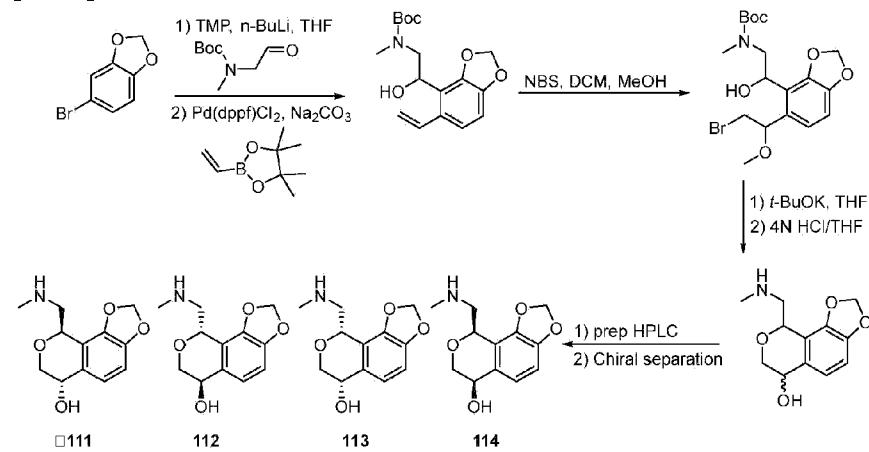
**[0444]** Compound 101 hydrochloride salt: Ret Time = 7.21 min; Enantiopurity: 100% ee. MS (ESI): *m/z* 258 [M + H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  7.17 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 5.24 (d, *J* = 8.8 Hz, 1H), 4.27-4.22 (m, 1H), 3.92-3.86 (m, 1H), 3.67-3.63 (m, 1H), 3.47-3.41 (m, 1H), 3.02-2.98 (m, 1H), 2.84 (t, *J* = 4.0 Hz, 1H), 2.80 (s, 3H).

**[0445]** Compound **102** hydrochloride salt: Ret Time = 4.997 min; Enantiopurity: 100% ee. MS (ESI): *m/z* 258 [M + H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  7.17 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 5.24 (d, *J* = 9.2 Hz, 1H), 4.27-4.22 (m, 1H), 3.92-3.86 (m, 1H), 3.67-3.63 (m, 1H), 3.47-3.41 (m, 1H), 3.02-2.98 (m, 1H), 2.84 (t, *J* = 3.6 Hz, 1H), 2.81 (s, 3H).

#### General Procedure M

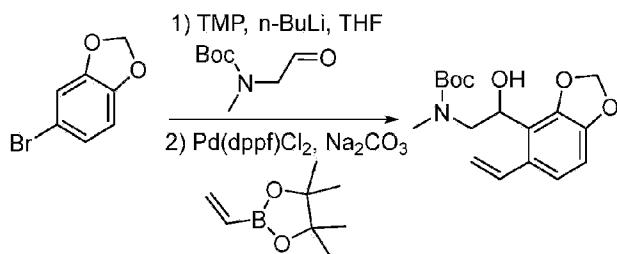
**13.1 Preparation of (6*S*,9*R*)-9-((methylamino)methyl)-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-6-ol (111), (6*R*,9*S*)-9-((methylamino)methyl)-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-6-ol (112), (6*S*,9*S*)-9-((methylamino)methyl)-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-6-ol (113) and (6*R*,9*R*)-9-((methylamino)methyl)-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-6-ol (114) (reference examples).**

#### [0446]



**(a). *tert*-butyl (2-((*tert*-butyldimethylsilyl)oxy)-2-(5-vinylbenzo[d][1,3]dioxol-4-yl) ethyl (methyl)carbamate**

#### [0447]



**[0448]** To a solution of 2,2,6,6-tetramethylpiperidine (TMP) (4.60 g, 32.6 mmol) in THF (50 mL) was added n-BuLi (2.5 N) (1.92 g, 30.1 mmol) dropwise at -78 °C under nitrogen. After stirring for 1 h, a solution of 5-bromobenzo[d][1,3]dioxole (5.06 g, 25.1 mmol) in THF (10 mL) was added and stirred at this temperature for another 2 h, then a solution of tert-butyl methyl(2-oxoethyl)carbamate (5.21 g, 30.1 mmol) in THF (10 mL) was added. The mixture was stirred at this temperature for 2 h. The mixture was quenched with water, extracted with EtOAc, dried and concentrated *in vacuo*. Purification by silica gel chromatography (petroleum ether:EtOAc 10:1) provided tert-butyl (2-(5-bromobenzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl) (methyl)carbamate. MS(ESI) *m/z*: 300[M-56-17]<sup>+</sup>, purity: 78%, 214 nm; 8.0 g yellow oil obtained, yield: 66.4%.

**[0449]** To a solution of tert-butyl (2-(5-bromobenzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl) (methyl)carbamate (800 mg, 2.13 mmol) in dioxane/water = 4/1 (10 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (589 mg, 3.83 mmol), Pd(dppf)Cl<sub>2</sub> (155 mg, 213 μmol) and Na<sub>2</sub>CO<sub>3</sub> (563 mg, 5.32 mmol) under nitrogen. The mixture was heated to 105 °C with stirring for overnight. The mixture was evaporated *in vacuo* to get the residue, diluted in water, extracted with DCM, dried and concentrated *in vacuo*. Purification by silica gel chromatography (petroleum ether:EtOAc = 5:1) provided tert-butyl 2-hydroxy-2-(5-vinylbenzo[d][1,3]dioxol-4-yl)ethyl(methyl) carbamate (500 mg, yield: 67%; purity: 92%) as a light yellow oil. MS(ESI): *m/z* 248 [M-56-17]<sup>+</sup>.

**(b).tert-butyl-2-(5-(2-bromo-1-methoxyethyl)benzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl(methyl)carbamate**

**[0450]**

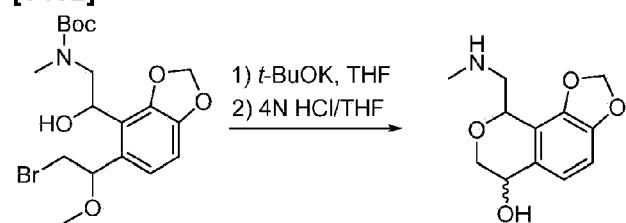


**[0451]** To a solution of tert-butyl (2-hydroxy-2-(5-vinylbenzo[d][1,3]dioxol-4-yl)ethyl) (methyl)carbamate (1.8 g, 5.6 mmol) in MeCN/MeOH = 1:1 (20 mL) was added NBS (1.09 g,

6.16 mmol) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 2 h. The mixture was quenched with water, evaporated *in vacuo* to get the residue, extracted with DCM, dried and concentrated under reduced pressure to get tert-butyl 2-(5-(2-bromo-1-methoxyethyl)benzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl(methyl)carbamate (1.2 g, yield: 42%, purity: 86%) as a yellow oil. MS(ESI): *m/z* 300, 302 [M-31-100]<sup>+</sup>.

**(c). 9-((methylamino)methyl)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-6-ol**

**[0452]**



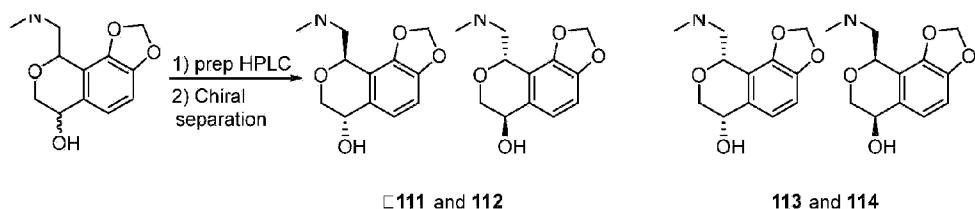
**[0453]** To a solution of tert-butyl (2-(5-(2-bromo-1-methoxyethyl)benzo[d][1,3]dioxol-4-yl)-2-hydroxyethyl)(methyl)carbamate (1.2 g, 2.77 mmol) in THF (15 mL) was added t-BuOK (620 mg, 5.54 mmol) at 0 °C. The mixture was then allowed to warm to room temperature and stirred overnight. The mixture was quenched with water, evaporated *in vacuo* to get the residue, extracted with DCM, dried and concentrated under reduced pressure. Purification by silica gel chromatography (petroleum ether:EtOAc 3: 1) provided tert-butyl (6-methoxy-7,9-dihydro-6H-[1,3]dioxolo[4,5-h]isochromen-9-yl) methyl(methyl)carbamate (600 mg; yield: 53%; purity: 86%) as a yellow solid. MS(ESI): *m/z* 374 [M+Na]<sup>+</sup>.

**[0454]** To a solution of tert-butyl ((6-methoxy-7,9-dihydro-6H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methyl)(methyl)carbamate (540 mg, 1.53 mmol) in THF (6 mL) was added HCl (6.0 N aq, 2.55 mL, 15.3 mmol) at room temperature. The mixture was stirred at room temperature overnight. The mixture was filtered, then the filtration was basified with 2 N aq. NaOH, extracted with DCM/MeOH, dried and concentrated *in vacuo* to provide crude 9-((methylamino)methyl)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-6-ol as a light brown oil (500 mg; yield: 69%; purity: 50%). MS(ESI): *m/z* 238 [M+H]<sup>+</sup>.

**(d). Trans isomers (6S,9R)-9-((methylamino)methyl)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-6-ol and (6R,9S)-9-((methylamino)methyl)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-6-ol (111 and 112), Cis isomers (6S,9S)-9-((methylamino)methyl)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-6-ol and (6R,9R)-9-((methylamino)methyl)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-6-ol (113 and 114).**

**[0455]**





**[0456]** The mixture of four isomers was separated into racemic mixtures of the cis and trans isomers by prep-HPLC in 0.01% aq.  $\text{NH}_4\text{HCO}_3$ . The mixture was separately freeze-dried to dryness. MS(ESI):  $m/z$  238 [M+H]<sup>+</sup>. P1, purity: 98%, 214 nm; 75 mg white solid obtained, yield: 14.7%. P2, purity: 93%, 214 nm; 140 mg white solid obtained, Yield: 26%.

[0457] The racemic mixture of trans isomers (**111** and **112**) was purified by chiral separation using Instrument: Gilson-281, Column: OZ 20 x 250, 10 um, Mobile Phase: n-Hex(0.1%DEA):EtOH(0.1%DEA) = 8:2 and Run time per injection: 10 mins to get the two isomers. The mixture was separately evaporated *in vacuo* to get the two desired products. MS(ESI): *m/z* 238 [M+H]<sup>+</sup>.

[0458] Trans isomer Peak 1 Compound **111**: Retention time 8.70 min. Purity: 99%, ee%: 99%, 90 mg white solid obtained, Yield: 30%.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.90 (d,  $J$  = 8.0 Hz, 1H), 6.79 (d,  $J$  = 7.6 Hz, 1H), 6.03 (s, 1H), 5.94 (s, 1H), 5.02 (t,  $J$  = 3.6 Hz, 1H), 4.45 (s, 1H), 4.15 (dd,  $J$  = 2.0/11.6 Hz, 1H), 3.77 (d,  $J$  = 11.6 Hz, 1H), 3.16-3.05 (m, 2H), 2.75 (brs, 2H), 2.37 (s, 3H).

**[0459]** Trans isomer Peak 2 Compound 112: Retention time 11.03 min. Purity: 100%, ee%: 100%, 70 mg white solid obtained, Yield: 23%.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.91 (d,  $J$  = 8.0 Hz, 1H), 6.80 (d,  $J$  = 8.0 Hz, 1H), 6.04 (d,  $J$  = 1.2 Hz, 1H), 5.95 (d,  $J$  = 1.2 Hz, 1H), 5.02 (t,  $J$  = 3.2 Hz, 1H), 4.45 (s, 1H), 4.15 (dd,  $J$  = 2.0/11.6 Hz, 1H), 3.78 (d,  $J$  = 11.2 Hz, 1H), 3.16-3.05 (m, 2H), 2.38 (s, 3H), 2.21 (brs, 2H).

[0460] The racemic mixture of cis isomers (**113** and **114**) was purified by chiral separation using Instrument: Gilson-281, Column: OZ 20 × 250, 10 um, Mobile Phase: n-Hexane (0.1%DEA):EtOH (0.1%DEA) = 8:2 and Run time per injection: 10mins to get the two isomers. The mixture was separately evaporated *in vacuo* to get the two desired products. MS(ESI): *m/z* 238 [M+H]<sup>+</sup>.

**[0461]** Cis isomer Peak 1 Compound **113**: Retention time: 15.52 min. Purity: 100%, ee%: 100%, 320 mg white solid obtained, Yield: 67%.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.99 (d,  $J$  = 8.0 Hz, 1H), 6.79 (d,  $J$  = 8.0 Hz, 1H), 5.99 (d,  $J$  = 1.2 Hz, 1H), 5.92 (d,  $J$  = 1.2 Hz, 1H), 5.02 (dd,  $J$  = 3.2, 8.8 Hz, 1H), 4.54 (t,  $J$  = 4.0 Hz, 1H), 4.09 (dd,  $J$  = 3.2, 11.6 Hz, 1H), 3.77 (dd,  $J$  = 4.4, 12.0 Hz, 1H), 3.01-2.91 (m, 2H), 2.5 (s, 3H), 2.13 (brs, 2H).

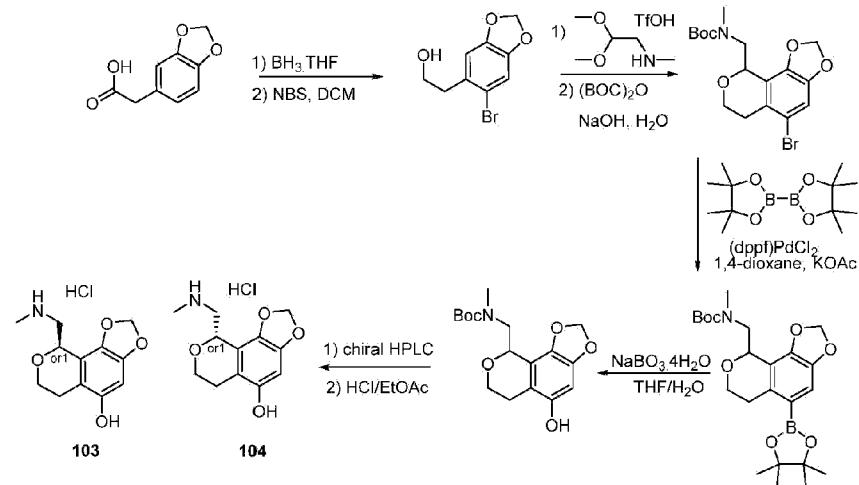
[0462] Cis isomer Peak 2 Compound 114: Retention time: 21.12 min. Purity: 100%, ee%:

100%, 340 mg white solid obtained, yield: 71%.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.99 (d,  $J$  = 8.0 Hz, 1H), 6.79 (d,  $J$  = 8.0 Hz, 1H), 5.99 (d,  $J$  = 1.2 Hz, 1H), 5.92 (d,  $J$  = 1.2 Hz, 1H), 5.02 (dd,  $J$  = 3.2, 8.8 Hz, 1H), 4.54 (t,  $J$  = 4.0 Hz, 1H), 4.09 (dd,  $J$  = 3.2, 11.6 Hz, 1H), 3.77 (dd,  $J$  = 4.4, 12.0 Hz, 1H), 3.01-2.91 (m, 2H), 2.5 (s, 3H), 2.13 (brs, 2H).

### General Procedure N

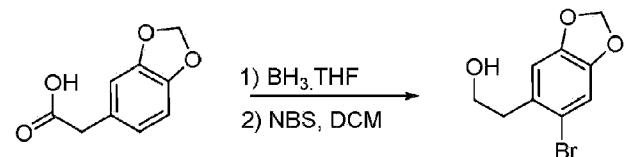
#### 14.1 Preparation of (R)-9-((methylamino)methyl)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-5-ol (103) and (S)-9-((methylamino)methyl)-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-5-ol (104) (reference examples)

[0463]



#### (a). 2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethan-1-ol

[0464]



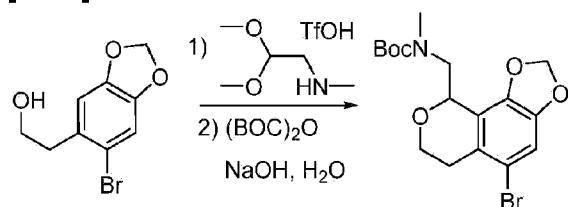
[0465] A solution of 2-(benzo[d][1,3]dioxol-5-yl)acetic acid (20 g, 111 mmol) in  $\text{BH}_3\text{/THF}$  (166 mL, 1.0 M, 166 mmol) was stirred at ambient temperature until the reaction was complete (~4h). The mixture was then poured into ice water and extracted with  $\text{EtOAc}$ , dried and concentrated. The crude was purified by silica gel (petroleum ether:  $\text{EtOAc}$  20:1 to 10: 1) to provide 2-(benzo[d][1,3]dioxol-5-yl)ethanol (16.5 g, yield=89.6%) as a colorless oil. MS (ESI):

*m/z* 149 [M-18+1]+.

**[0466]** To a solution of 2-(benzo[d][1,3]dioxol-5-yl)ethanol (16.5 g, 99.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added NBS (19.2 g, 109 mmol), and the reaction was stirred at ambient temperature until complete (~4 h). The mixture was then washed with NaHSOs solution, brine and dried. The crude product was used in the next step without further purification. 21g (yield: 100%). MS (ESI): *m/z* 227, 229 [M-18+1]+.

**(b). *tert*-butyl ((5-bromo-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-9-yl) methyl) (methyl)carbamate**

**[0467]**

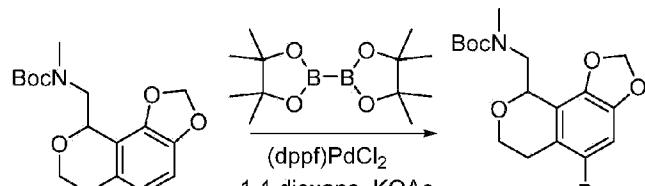


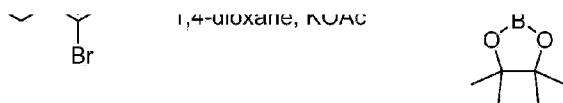
**[0468]** To a solution of 2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethanol (8 g, 32.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added 2,2-dimethoxy-*N*-methylethanamine (7.76 g, 65.2 mmol) and trifluoromethanesulfonic acid (14.6 g, 97.8 mmol) at 0 °C. The reaction was then stirred at ambient temperature until complete (~16 h). The mixture was used in the next step without further purification.

**[0469]** To a solution of 1-(5-bromo-7,9-dihydro-6H-[1,3]dioxolo[4,5-h]isochromen-9-yl)- *N*-methylmethanamine (2 g, 6.66 mmol) in H<sub>2</sub>O (50 mL) was added NaOH (2.12 g, 53.2 mmol) and di-*tert*-butyl dicarbonate (1.74 g, 7.99 mmol) at 0 °C. The reaction was stirred at ambient temperature until complete (~16 h). EtOAc (100 mL) was added and the reaction was washed with saturated aqueous NH<sub>4</sub>Cl, then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with petroleum ether:EtOAc 5:1 to afford the title compound. MS (ESI): *m/z* 300, 302 [M-100+H]+.

**(c). *tert*-butyl methyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,9-dihydro- 7H-[1,3]dioxolo[4,5-h]isochromen-9-yl)methyl)carbamate**

**[0470]**

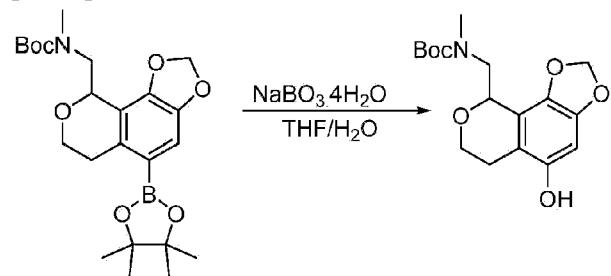




**[0471]** To a solution of *tert*-butyl ((5-bromo-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate (12 g, 29.9 mmol) in 1,4-dioxane (150 mL) was added 4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.59 g, 29.9 mmol), KOAc (5.86 g, 59.8 mmol) and Pd(dppf)Cl<sub>2</sub> (1.08 g, 1.49 mmol). The reaction mixture was stirred and heated to 100 °C until complete (~16 h). The reaction mixture was then concentrated, then water and EtOAc were added. The combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with petroleum ether:EtOAc 20:1 to afford *tert*-butyl methyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)carbamate, 10.0 g, yield=75.1%. MS (ESI): *m/z* 348 [M-100+H]<sup>+</sup>.

**(d). *tert*-butyl ((5-hydroxy-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl) methyl) (methyl)carbamate**

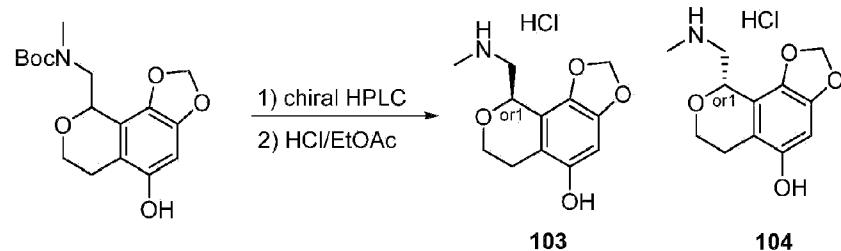
**[0472]**



**[0473]** To a solution of *tert*-butyl methyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)carbamate (8.0 g, 17.8 mmol) in THF/H<sub>2</sub>O (100 mL/ 40 mL) was added NaBO<sub>3</sub>·4H<sub>2</sub>O (8.22 g, 53.4 mmol). The reaction was stirred at ambient temperature until complete (~3 h). The reaction was concentrated, then water and EtOAc were added. The layers were separated and the aqueous phase was washed with EtOAc. The combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*, purified by silica chromatography (petroleum ether:EtOAc 5: 1) to provide *tert*-butyl((5-hydroxy-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl) (methyl)carbamate as a white solid (3.4 g, yield: 57%). MS (ESI): *m/z* 338 [M+H]<sup>+</sup>.

**(e). (*R*)-9-((methylamino)methyl)-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*]isochromen-5-ol (103) and (*S*)- 9-((methylamino)methyl)-6,9-dihydro-7*H*-[1,3]dioxolo[4,5-*h*] isochromen-5-ol (104)**

[0474]



**[0475]** Tert-butyl((5-hydroxy-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate (1.5 g, 4.44 mmol) was separated into its enantiomers (*R*)-*tert*-butyl ((5-hydroxy-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate and (*S*)-*tert*-butyl ((5-hydroxy-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate by Gilson-281 using AY 20\*250, 10um and mobile phase Hexane(0.1%DEA):EtOH(0.1%DEA)=95:5. Flow rate = 50 mL/min. (*R*)-*tert*-butyl ((5-hydroxy-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate(0.6 g, Yield =40.2%) was obtained as white solid and (*S*)-*tert*-butyl ((5-hydroxy-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate (0.6 g, Yield =40.2%) was obtained as white solid.

**[0476]** To a solution of (*A*)-*tert*-butyl ((5-hydroxy-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate (0.32 g, 948  $\mu$ mol) in EtOAc (10 mL) was added HCl/EtOAc (1.5 mL, 3.0 M, 4.73 mmol). The reaction was stirred at ambient temperature for 4 h. Filtration afforded compound **103** hydrochloride salt as a white solid (0.18 g, yield: 78.5%). Chiral HPLC: Column AY-H (250\*4.6 mm, 5 um; Mobile Phase: n-Hexane (0.1% DEA):EtOH (0.1% DEA) = 80:20; Temp = 40 °C; Flow rate = 1.0 mL/min; Ret Time = 5.39 min; Enantiopurity: 100% ee. MS (ESI): *m/z* 238 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  6.4 (s, 1H), 5.92 (s, 1H), 5.87 (s, 1H), 5.07- 5.04 (m, 1H), 4.22-4.17 (m, 1H), 3.82-3.76 (m, 1H), 3.66-3.63 (m, 1H), 3.42-3.37 (m, 1H), 2.75 (s, 3H), 2.68 (t, 2H).

**[0477]** To a solution of (*S*)-*tert*-butyl ((5-hydroxy-7,9-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]isochromen-9-yl)methyl)(methyl)carbamate (0.35 g, 1.03 mmol) in EtOAc (5 mL) was added HCl/EtOAc (1.7 mL, 3.0 M, 5.15 mmol). The reaction was stirred at ambient temperature for 4 h. Filtration afforded compound **104** hydrochloride salt as a white solid (0.19 g; yield: 76.2%). Chiral HPLC: Column AY-H (250\*4.6 mm, 5 um; Mobile Phase: n-Hexane (0.1% DEA):EtOH (0.1% DEA) = 80:20; Temp = 40 °C; Flow rate = 1.0 mL/min; Ret Time = 6.05 min; Enantiopurity: 100% ee. MS (ESI): *m/z* 238 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, methanol-*d*<sub>4</sub>):  $\delta$  6.4 (s, 1H), 5.92 (s, 1H), 5.87 (s, 1H), 5.07- 5.04 (m, 1H), 4.22-4.17 (m, 1H), 3.82-3.76 (m, 1H), 3.66-3.63 (m, 1H), 3.42-3.37 (m, 1H), 2.75 (s, 3H), 2.68 (t, 2H).

**Example 115**

## Biological Assays

### Neuropharmacological Assay (SmartCube™)

**[0478]** In order to demonstrate the utility of the provided compounds to treat neurological and psychiatric diseases and disorders, exemplary compounds were evaluated using the neuropharmacological screen described in S.L. Roberds et al., *Front. Neurosci.* 2011 Sep 9;5:103 (doi: 10.3389/fnins.2011.00103) ("Roberds"). As reported in *Roberds*, because psychiatric diseases generally result from disorders of cell-cell communication, circuitry, intact systems are useful in detecting improvement in disease-relevant endpoints. These endpoints are typically behavioral in nature, often requiring human observation and interpretation. To facilitate testing of multiple compounds for behavioral effects relevant to psychiatric disease, PsychoGenics, Inc. (Tarrytown, NY, "PGI") developed SmartCube™, an automated system in which behaviors of compound-treated mice are captured by digital video and analyzed with computer algorithms. (D. Brunner et al., *Drug Discov. Today* 2002, 7:S107-S112). PGI Analytical Systems uses data from SmartCube™ to compare the behavioral signature of a test compound to a database of behavioral signatures obtained using a large set of diverse reference compounds. (The composition of the database as well as validation of the method is further described in *Roberds*). In this way, the neuropharmacological effects of a test compound can be predicted by similarity to major classes of compounds, such as antipsychotics, anxiolytics and antidepressants.

**[0479]** The SmartCube™ system produces an activity signature indicating the probability that the activity of the test compound at the administered dose matches a given class of neuropharmacological agents. (See, e.g., *Roberds*, Figures 2 and 3). The test compound is simultaneously compared against multiple classes of agents; thus, a separate probability is generated for each behavioral effect measured (e.g., anxiolytic activity, analgesic activity, etc.). In the table below, these probabilities are reported for each behavioral effect measured as follows:

LOQ ≤	+	< 5 %
5% ≤	++	< 25 %
25% ≤	+++	< 50 %
50% ≤	++++	

where LOQ is the limit of quantification.

**[0480]** Provided compounds were dissolved in a mixture of Pharmasolve™ (*N*-methyl-2-pyrrolidone), polyethylene glycol and propylene glycol, and were injected i.p. 15 min. before the behavioral test. For each compound, injections were administered at 3 different doses. For each behavioral effect measured, results for the most efficacious dose(s) are presented. In the

table below, DP: anti-depressant; AX: anxiolytic; SD: sedative hypnotic; PS: anti-psychotic; MS: mood stabilizer; AD: ADHD; CE: cognitive enhancer; AG: analgesic; UN: uncharacterized CNS activity.

**[0481]** The potency of many of the compounds in the table was also determined in the SmartCube™ system. Test compounds were routinely examined at dose levels of 0.3, 1, 3 10 and 30 mg per kg (mpk), although the dose range was increased or decreased if necessary to obtain a full dose response curve. A compound's minimal effective dose (MED) is a measure of the compounds potency. The MED was defined as the dose (in mpk) having 50% or more total activity in SmartCube. The potencies of the compounds are shown in the table below, with potency values in mpk binned in the following manner:

MED mpk range		BIN									
≤3 mpk		A									
>3 to 10 mpk		B									
>10 to ≤30 mpk		C									
>30 mpk		D									
Ex.	DP	AX	SD	PS	MS	AD	CE	AG	UN	POTENCY	
1	++++	++	++	++	+	+	+	+	+	A	
2	+++	++	+	++	++	+	++	++	+++	A	
3	+++	++	+	+	+	++	+	++	+	C	
4	++++	+	+	+	+	+	+	++	+	B	
5	+	++	+	+	+	+	+	++	+	D	
6	+	++	+	++	++	+	+	+	++++	C	
7	++	+++	+	++	++	++	++	+++	++	A	
8	++	++	+	++	+	+	++	++	+++	B	
9	+++	++	++	++	++	+	+	++	+++	B	
10	++	++	+	++	+	+	++	+	+++	C	
11	++++	+	+	+	+	++	+	+	+	B	
12	++++	+	++	++	+	+	+	++	++	B	
13	++	++	++	+	+	+	+	++	+++	C	
14	++++	++	++	++	++	+	++	++	+++	A	
15	++	++	++	+++	++	+	++	++	+++	A	
16	++	++	++	+++	+	+	+	++	+	C	
17	++	++	+	+++	+	+	+++	++	++	A	
18	++	++	+	+	+	+	++	++	++	C	
19	++	++	+	++	++	+	++	++	++	B	
20	++	++	++	++++	+	+	++	+	++++	A	

Ex.	DP	AX	SD	PS	MS	AD	CE	AG	UN	POTENCY
21	++	++	++	++	+	+	++	+++	+++	B
22	+++	++	++	+++	++	+	++	++	+	A
23	++	++	++	+++	+	+	++	++	+	B
24	++	++	++	+++	+	+	++	++	+++	A
25	+++	+	++	++	+	+	++	++	+	B
26	++++	++	++	++	+	+	++	++	+++	A
27	++	++	+	+	+	+	++	++	+++	C
28	++	++	++	+++	+	+	++	++	+++	A
29	++++	++	+	+	+	+	++	++	++	B
30	++	++	++	++	+	+	++	++	+++	B
31	++++	++	+	+	+	+	++	++	+	A
32	++	++	+	++	+	+	++	+	+	C
33	++++	++	++	+	+	+	++	++	+++	A
34	++	++	+	+++	++	+	++	++	+++	A
35	++++	++	++	++	+	++	++	++	++++	A
36	+	++	+	++	+	+	++	+	+++	B
37	++	+	+	++	+	+	++	++	++++	A
38	++	++	++	++	+	+	+	++	+++	A
39	++++	++	+	++	+	+	++	++	+++	A
40	++	+++	++	++	+	+	+	+	+++	A
41	++	++	++	++++	+	+	+	++	++++	A
42	++	+	+	+	+	+	++	++	++	C
43	+	++	+	++	+	+	++	++	++++	C
44	+	++	+	++	+	+	++	++	+++	B
45	+	++	+	++	+	+	++	++	++++	B
46	++	++	++	++	+	+	++	+	+++	B
47	++++	++	++	++	+	+	+	+	++	B
48	+	++	+	++	+	+	++	++	++++	A
49	++	++++	+	++	+	+	++	++	+++	A
50	+	++	+	+	+	+	+	++	++++	C
51	+	+++	+	++	+	+	++	++	+++	B
52	++	++	++	++	+	+	++	+++	++++	B
53	++++	++	+	+	+	++	++	++	+	A
54	+	++	++	++	+	+	++	+	++++	B
55	++	++	+	+	+	+	+	++	++++	C

Ex.	DP	AX	SD	PS	MS	AD	CE	AG	UN	POTENCY
56	+	++	++	++	+	+	++	++	++++	A-B
57	+	++	+	+	+	+	++	++	+++	D
60	++	++	++++	++	+	+	+	+	+++	B
61	+	++	+	++++	+	+	+	+	+++	B
62	+	++++	+	+	+	+	+	++	++	C
63	++++	++	++	+	+	++	+	+	++++	A-B
64	+	+++	++	++	+	+	++	++	++++	A-B
65	++	++	++	++	+	+	+	++	++++	A-B
66	++++	++	+	+	+	+	+	+	+	A-B
67	++++	++	+	++	+	+	+	+	+	A-B
93	++	+++	++	+	+	+++	++	++	++++	A
92	++	++	++	+	+	+	++	++	+++	C
74	+	++	++	+	+	+	+	+	+++	C
75	++	++	+	++	+	+	++	++	++++	B
71	+	++	+	++	+	+	++	++	++++	A
70	++	++	++	+++	+	+	++	++	+++	B
88	++	++	++	++	+	+	++	++	++	B
89	++	++	+	++	+	+	+++	++	++++	A
79	++++	+	++	+	+	++	+	+	+	A
78	++	++	+	+	+	+	+	++	++++	C
98	+	+	+	+	+	+	+	+	+	D
99	+	++	++	++	+	+	+	+	+++	C
86	++	++	+++	++	+	++	++	+	+	C
87	++	++	+	++	+	+	+	++	++++	A
90	++	++	+++	++	+	+	++	++	+++	A
91	+	+	+	++	+	+	+	++	++++	C
96	+	+	+++	+	+	+	+	+	+	C
97	+++	++	+	++	+	++	+	+	+++	B
85	++	+++	++	++	+	+	++	+	+++	A
84	++	++	++	++	+	+	++	++	++++	A
69	++	++	+	++	++	++	+	+++	++++	A
68	++	++	+++	++	+	+	++	++	++	B
81	++++	++	+	+	+	++	+	+	++	A
80	++	++	+	+++	+	+	++	+	+	C

Ex.	DP	AX	SD	PS	MS	AD	CE	AG	UN	POTENCY
72	++	++	+	+	+	+	+	+	+++	B
73	+++	++	++	+	+	+	++	+	++++	A
101	+	++	+	++	+	+	++	+++	+	B
102	++	++	+	+	+	+	+	++	+++	C
103	+	+	+	+	+	+	+	+	+	D
104	++++	+++	++	+	+	+	++	+	++	A
105	++	++	+++	++	+	+	+	+	+	A
106	++	++	++	++	+	+	+++	+	+	C
107	++	++	++	++	+	+	+	+	+++	B
108	++	+	+	++	+	+	+	+	++++	B
109	++	++	++	++++	+	+	+	+	++	B
110	++	++	+++	++	+	+	++	+	+	B
111	++++	++	+	++	+	+	+	+	+	C
112	++	++	+	+	+	+	+	+	+	D
113	+	++	+	+	+	+	+	+	+	D
114	+	++	+	++	+	+	+	+	+++	C

### Example 116

### Additional Rodent Tests

### Forced Swim Test Procedures

**[0482]** The Forced Swim test (FST) is an indicator of the antidepressant-like activity of a test compound. Male Balb/cJ mice (26-31g) were given a 30 minute pretreatment with vehicle (sterile water), sertraline control or test compound. The FST consists of one 6 minute session of forced swimming in individual opaque cylinders containing water at a temperature of  $23 \pm 2$  °C. The mouse will swim before "giving up" and becoming immobile, the time spent immobile was recorded over the 6 minute trial. A compound with antidepressant-like activity will decrease the time the mouse is immobile over the 6 minute trial. Data were analyzed by analysis of variance (ANOVA) followed by post-hoc comparisons with Fisher Tests when appropriate. Data is shown in Figures 1a and 1b.

### Phencyclidine (PCP)-Induced Hyperlocomotion

**[0483]** The PCP-induced hyperlocomotion assay is an indicator of antipsychotic-like activity. Male C57Bl/6J mice (20-26g) were administered vehicle or test compound and placed in holding cages for 30 minutes, after which they were placed in the locomotor activity chambers for 30 minutes of baseline capture. The test chambers are Plexiglas rectangular chambers (24 x 45 cm) that fit inside two steel frames (9.5 x 18 inches) and are fitted with two-dimensional 4 x 8 beam grids to monitor horizontal and vertical locomotor activity. Total distance traveled was measured from horizontal beam breaks as the animal traveled. Following the 30 minute baseline period, all rats were injected with saline or PCP (2.5 mg/kg, s.c.) and returned to the locomotor activity chambers for a 60 minute test session. A compound with antipsychotic-like activity will decrease the distance traveled following administration of PCP. Data were analyzed by analysis of variance (ANOVA) followed by post-hoc comparisons with Fisher Tests when appropriate. Data is shown in Figures 2a and 2b.

#### **Amphetamine-Induced Hyperlocomotion Assay**

**[0484]** Amphetamine (AMPH) is frequently used to induce or mimic a manic-like state. The antimanic-like effects of test compounds were evaluated in male C57Bl/6J mice. Mice were acclimatized to the experimental room for at least 1 hour prior to testing. The mice (n=10 per group) were administered vehicle or test compound and placed in the open field (OF) chambers for 30 minutes of baseline activity measurement. The mice were then injected with either water or AMPH (4 mg/kg, ip) and placed back in the OF chambers for a 60-minute testing session during which, the effects of test compounds on stimulant-induced hyperactivity behaviors (total distance traveled, rearing and stereotypy) were measured. Data were analyzed by analysis of variance (ANOVA) followed by post-hoc comparisons with Fisher Tests when appropriate. Data is shown in Figures 3a to 3d.

#### **Tail Suspension Test**

**[0485]** The tail suspension test (TST) is a rodent screening test for potential (human) antidepressant drugs. It is based on the assumption that an animal will actively try to escape an aversive (stressful) stimulus. If escape is impossible, the animal will eventually stop trying ("give up"). In the TST, a mouse is suspended by the tail so that its body dangles in the air, head downward. Mice initially struggle to face upward and climb to a solid surface. When the animal stops struggling and hangs immobile it is considered to have "given up". Shorter periods of immobility are characteristic of antidepressant-like activity. Accordingly, longer periods of immobility are considered indicative of a depressive-like state. It has been shown that treatment with an antidepressant drug will decrease the time the animal spends immobile. See generally L. Steru et al., *Psychopharmacology (Berl)*. 1985;85(3):367-70; B. Thierry et al., *Psychopharmacology* 1986;90:284-85.

**[0486]** *Procedure.* Adult male AJ mice from Jackson Laboratories received vehicle (sterile water) or test compound orally by gavage, or the positive control desipramine (20 mg/kg, i.p.), in 10 mL/kg injection volumes, 30 min before being subjected to the Tail Suspension Test. In this test, mice are placed in the Tail Suspension chambers (white polyvinylchloride cubicles measuring 33 × 33 × 31.75 cm *Med Associates, Inc.* St. Albans, VT) by a piece of transparent (Scotch®) tape attached to the tail, from about the mid-tail, with approximately 2 cm of tape past the end of the tail for 10 min during which the time spent immobile is measured. A reduction in total time immobile relative to the vehicle condition indicates an antidepressant drug-like response. Data is shown in Figures 4a to 4c.

**[0487]** Additional data for the tests in Example 116 are shown below:

**Data for additional rodent tests**

**[0488]**

Compound Example No.	PCP	AMPH	TST	FST
2	+++	NE	ND	+++
14	ND	+	+	ND
17	ND	++	NE	ND
26	+++	+	NE	+++

Efficacious dose: +++ = <1.0 mg/kg, ++ = 1-10 mg/kg, + = 10-30 mg/kg,  
ND = not determined, NE = no effect

## REFERENCES CITED IN THE DESCRIPTION

### Cited references

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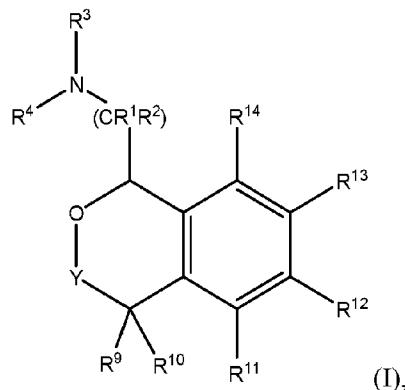
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**Patentkrav****1. Forbindelse med formel (I):**

5

eller et farmaceutisk acceptabelt salt deraf,

hvor:

Y er  $-\text{C}(\text{R}^5\text{R}^6)-$ ;

10  $\text{R}^1$  og  $\text{R}^2$  er valgt uafhængigt af H, alifatisk ( $\text{C}_1\text{-}\text{C}_8$ )carbonhydrat og ( $\text{C}_3\text{-}\text{C}_6$ )cycloalkyl, hvor den alifatiske ( $\text{C}_1\text{-}\text{C}_8$ )carbonhydrat eventuelt er substitueret med en eller flere af halogen, hydroxyl, ( $\text{C}_1\text{-}\text{C}_6$ )alkoxy, amino, ( $\text{C}_1\text{-}\text{C}_6$ )alkylamino og di( $\text{C}_1\text{-}\text{C}_6$ )alkylamino;

eller tilsammen kan  $\text{R}^1$  og  $\text{R}^2$  danne ( $\text{C}_3\text{-}\text{C}_6$ )cycloalkyl;

15  $\text{R}^3$  er hydrogen, og  $\text{R}^4$  er hydrogen eller methyl;

$\text{R}^5$  og  $\text{R}^6$  er begge hydrogen;

20  $\text{R}^9$  og  $\text{R}^{10}$  er valgt uafhængigt fra H, halogen, hydroxyl, ( $\text{C}_1\text{-}\text{C}_6$ )alkyl, ( $\text{C}_1\text{-}\text{C}_6$ )halogenalkyl og ( $\text{C}_1\text{-}\text{C}_6$ )alkoxy;

$\text{R}^{11}$ ,  $\text{R}^{12}$ ,  $\text{R}^{13}$  og  $\text{R}^{14}$  er valgt uafhængigt af H, fluor, chlor, iod, cyano og alifatisk ( $\text{C}_1\text{-}\text{C}_8$ )carbonhydrat,

med det forbehold at:

mindst en af  $\text{R}^{11}$ ,  $\text{R}^{12}$ ,  $\text{R}^{13}$  og  $\text{R}^{14}$  er andet end hydrogen.

2. Forbindelse ifølge krav 1, hvor R<sup>1</sup> er hydrogen, og R<sup>2</sup> er hydrogen eller methyl.

5 3. Forbindelse ifølge krav 1, hvor R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> og R<sup>14</sup> er valgt uafhængigt af hydrogen, fluor, chlor, alifatisk (C<sub>1</sub>-C<sub>8</sub>)carbonhydrat og cyano.

4. Forbindelse ifølge krav 1, hvor R<sup>9</sup> og R<sup>10</sup> er valgt uafhængigt blandt H, fluor og methyl.

10 5. Forbindelse ifølge krav 1, hvor:

a) en af R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> og R<sup>14</sup> er fluor, chlor, methyl eller cyano, og de resterende tre er H; eller:

b) to af R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> og R<sup>14</sup> er fluor, chlor, methyl eller cyano, og de resterende to er H.

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6. Forbindelse ifølge krav 5a), hvor R<sup>12</sup> og R<sup>13</sup> er H, en af R<sup>11</sup> og R<sup>14</sup> er valgt blandt fluor, chlor, methyl og cyano, og den anden af R<sup>11</sup> og R<sup>14</sup> er H.

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7. Forbindelse ifølge krav 5b), hvor R<sup>12</sup> og R<sup>13</sup> er H, og R<sup>11</sup> og R<sup>14</sup> er valgt blandt fluor, chlor, methyl og cyano.

8. Forbindelse ifølge krav 1, hvor R<sup>1</sup> er hydrogen; R<sup>2</sup> er hydrogen eller methyl; R<sup>3</sup> er hydrogen; R<sup>4</sup> er hydrogen eller methyl; R<sup>9</sup> og R<sup>10</sup> er brint.

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9. Forbindelse ifølge krav 8, hvor:

a) R<sup>12</sup> og R<sup>13</sup> er H, en af R<sup>11</sup> og R<sup>14</sup> er valgt blandt fluor, chlor, methyl og cyano, og den anden af R<sup>11</sup> og R<sup>14</sup> er H; eller:

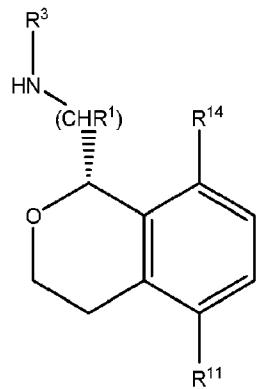
b) R<sup>12</sup> og R<sup>13</sup> er H, og R<sup>11</sup> og R<sup>14</sup> er valgt blandt fluor, chlor, methyl og cyano.

**10.** Forbindelse ifølge krav 9b), hvor  $R^{14}$  er valgt blandt fluor, chlor, methyl og cyano.

**11.** Forbindelse ifølge krav 1, hvor  $R^1$  er hydrogen;  $R^2$  er hydrogen eller methyl;  $R^9$  og  $R^{10}$  er hydrogen; og  $R^{14}$  er valgt blandt fluor, chlor, methyl og cyano, og  $R^{11}$ ,  $R^{12}$  og  $R^{13}$  er H.

**12.** Forbindelse ifølge krav 11, hvor:

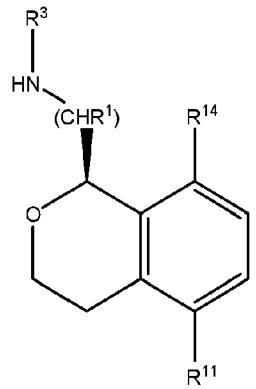
a) C(1) af isochromanen er af absolut konfiguration:



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eller et farmaceutisk acceptabelt salt deraf; eller:

b) C(1) af isochromanen er af absolut konfiguration:

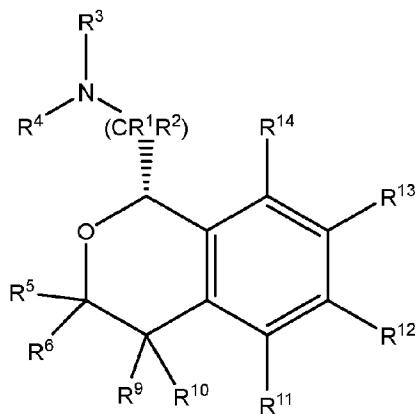


eller et farmaceutisk acceptabelt salt deraf.

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**13.** Forbindelsen ifølge krav 1, af:

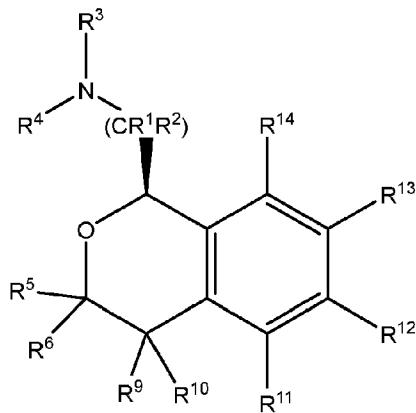
a) formel IIa:



IIa

eller et farmaceutisk acceptabelt salt deraf; eller:

5 b) formel IIb:



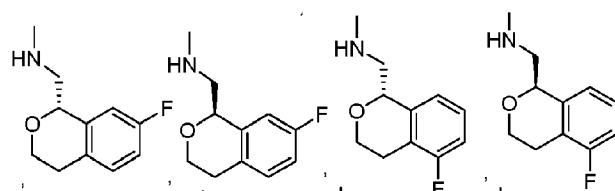
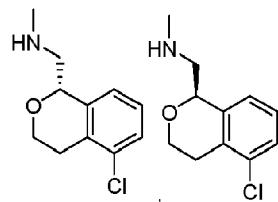
IIb

eller et farmaceutisk acceptabelt salt deraf.

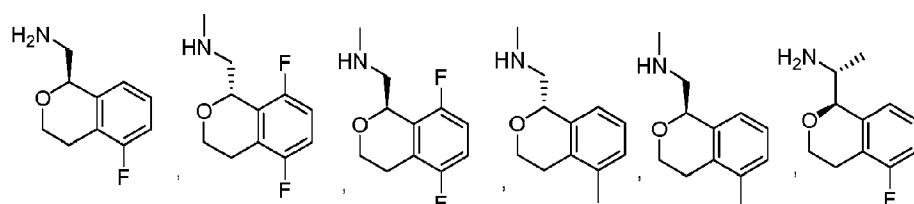
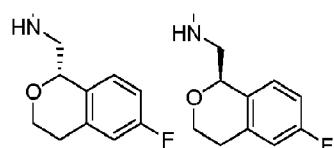
10 14. Forbindelse ifølge krav 1, hvor R<sup>1</sup> er hydrogen; R<sup>2</sup> er hydrogen eller methyl; R<sup>3</sup> er hydrogen; og R<sup>4</sup> er hydrogen eller methyl.

15. Forbindelse ifølge krav 14, hvor R<sup>9</sup> og R<sup>10</sup> hver især uafhængigt er hydrogen, methyl eller fluor, og hvor R<sup>4</sup> er hydrogen.

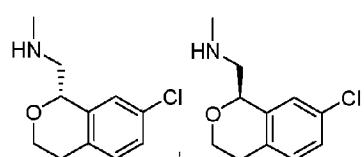
16. Forbindelse ifølge krav 1, hvor forbindelsen er:

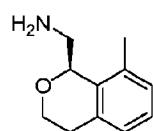
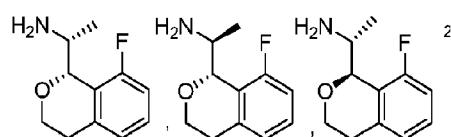
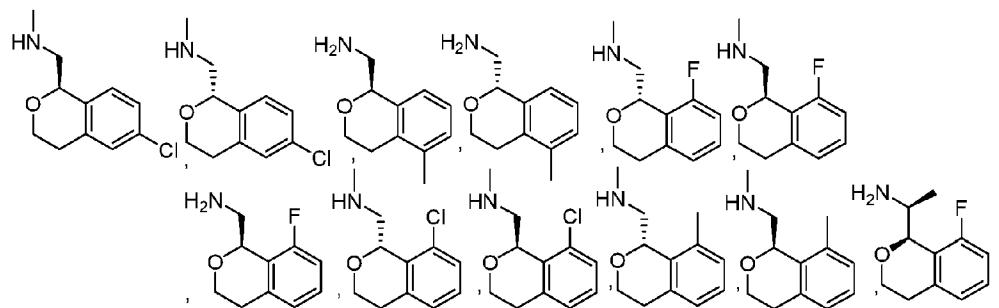


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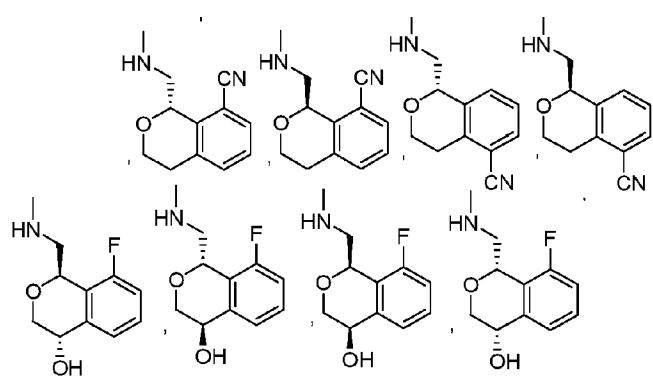
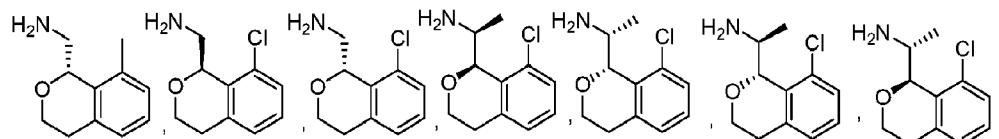


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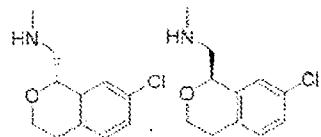




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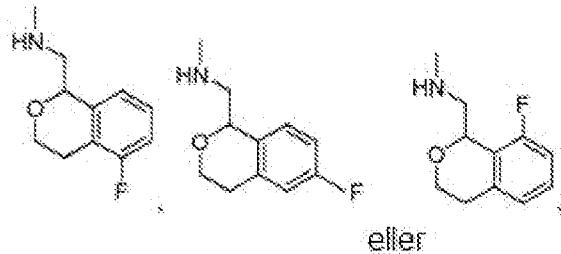


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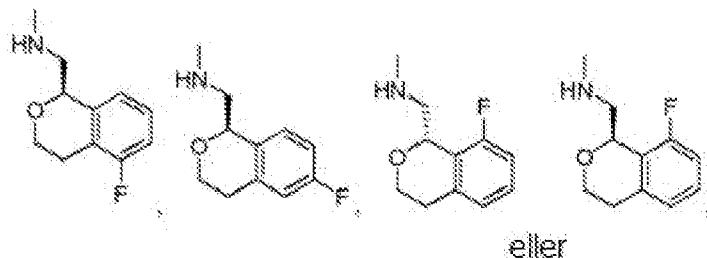


eller et farmaceutisk acceptabelt salt deraf.

17. Forbindelse ifølge krav 1, hvor forbindelsen er:

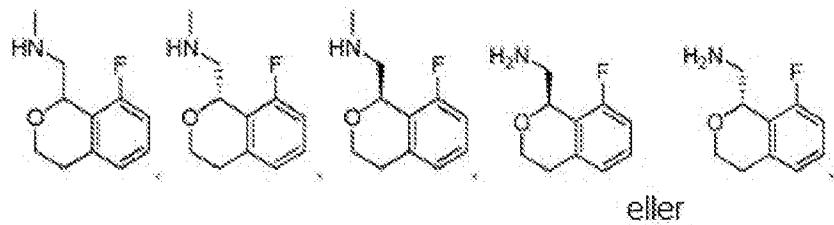


eller et farmaceutisk acceptabelt salt deraf; eventuelt hvor forbindelsen er:



5 eller et farmaceutisk acceptabelt salt deraf.

18. Forbindelse ifølge krav 1, hvor forbindelsen er:



eller et farmaceutisk acceptabelt salt deraf.

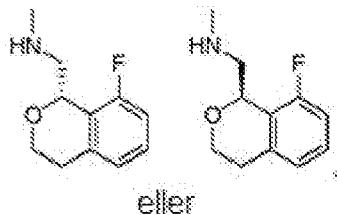
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19. Forbindelse ifølge krav 1, hvor forbindelsen er:



eller et farmaceutisk acceptabelt salt eller stereoisomer deraf.

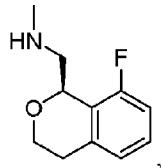
20. Forbindelse ifølge krav 1, eller et farmaceutisk acceptabelt salt deraf, valgt blandt:



eller en blanding deraf.

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21. Forbindelse ifølge krav 20, hvor forbindelsen er:



eller et farmaceutisk acceptabelt salt deraf.

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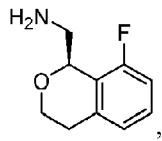
22. Forbindelse ifølge krav 20, hvor forbindelsen er:



eller et farmaceutisk acceptabelt salt deraf.

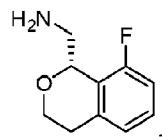
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23. Forbindelse ifølge krav 1, hvor forbindelsen er:



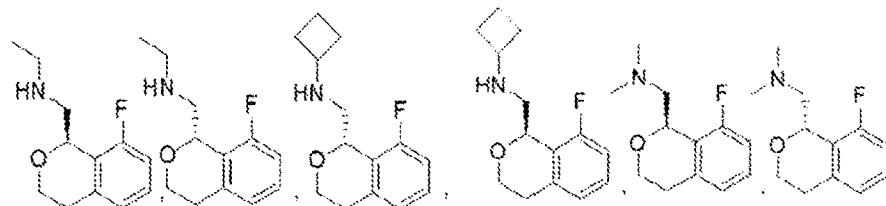
eller et farmaceutisk acceptabelt salt deraf.

**24.** Forbindelse ifølge krav 1, hvor forbindelsen er:



eller et farmaceutisk acceptabelt salt deraf.

5      **25.** Forbindelse valgt blandt:



**26.** Forbindelse eller farmaceutisk acceptabelt salt deraf ifølge et hvilket som

10      helst af kravene 1 til 18 eller krav 20 til 25, hvor forbindelsen eller saltet er:

- mere end 90% enantiomert ren; eller
- mere end 95% enantiomert ren.

15      **27.** Sammensætning, der omfatter forbindelsen ifølge et hvilket som helst af kravene 1 til 26 eller et farmaceutisk acceptabelt salt deraf og en farmaceutisk acceptabel bærer, adjuvans eller vehikel.

20      **28.** Forbindelse ifølge et hvilket som helst af kravene 1 til 26, eller et farmaceutisk acceptabelt salt deraf, eller en sammensætning ifølge krav 27, til anvendelse i behandlingen af en neurologisk eller psykiatrisk sygdom eller lidelse hos et individ med behov derfor.

25      **29.** Forbindelse eller farmaceutisk acceptabelt salt deraf eller sammensætning til anvendelse i en fremgangsmåde ifølge krav 28, hvor den neurologiske eller

psykiatriske sygdom eller lidelse er depression, bipolar lidelse, smerte, skizofreni eller andre psykotiske sygdomme, obsessiv-kompulsiv lidelse, afhængighed, social lidelse, opmærksomhedsunderskudshyperaktivitetsforstyrrelse, en angstlidelse, en bevægelsesforstyrrelse, epilepsi, autisme eller kognitiv sygdom eller lidelse, eventuelt hvor den neurologiske eller psykiatriske sygdom eller lidelse er depression.

**30.** Forbindelse eller farmaceutisk acceptabelt salt deraf eller sammensætning til anvendelse i en fremgangsmåde ifølge krav 28, hvor den neurologiske eller psykiatriske sygdom eller lidelse er:

a) er bipolar lidelse, angst, depression, Alzheimers sygdom med agitation, Alzheimers sygdom med aggression eller Alzheimers sygdom med agitation aggression; eller:

b) er bipolar lidelse, angst, depression, demens, Alzheimers sygdom, Alzheimers sygdom med agitation, Alzheimers sygdom med aggression eller Alzheimers sygdom med agitation og aggression, en neurokognitiv lidelse, en neurokognitiv lidelse med adfærdsmæssige og psykologiske symptomer; eller:

c) psykose, herunder skizofreni (paranoid, uorganiseret, katatonisk eller udifferentieret), skizofreniform lidelse, skizoaffektiv lidelse, vrangforestillingslidelse, kortvarig psykotisk lidelse, delt psykotisk lidelse, psykotisk lidelse på grund af en generel medicinsk tilstand og stof-induceret eller narkotika-induceret psykosepsykotisk sygdom lidelse, psykose forbundet med affektive lidelser, kortvarig reaktiv psykose, skizoaffektiv psykose, "skizofreni-spektrum" lidelser såsom skizoide eller skizotypiske personlighedsforstyrrelser eller sygdom forbundet med psykose (såsom svær depression, maniodepressiv (bipolar) lidelse, Alzheimers sygdom og posttraumatisk stresssyndrom), inklusive både positive, negative og kognitive symptomer på skizofreni og andre psykoser; kognitive lidelser, herunder demens (semantisk demens, frontotemporal demens, demens med depressive træk, vedvarende, subkortikal demens, demens med Lewy Bodies, Parkinsonism-ALS Demens Complex og demens for-

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bundet med Alzheimers sygdom, iskæmi, multi-infarkt demens, traumer, va-  
skulære problemer, slagtilfælde, HIV-sygdom, Parkinsons sygdom, Hunting-  
tons sygdom, Downs syndrom, Picks sygdom, Creutzfeldt-Jacobs sygdom, pe-  
rinatal hypoxi eller stofmisbrug), delirium, amnestiske lidelser eller aldersrela-  
5 teret kognitiv tilbagegang; angstlidelser inklusive akut stresslidelse, agorafobi,  
generaliseret angstlidelse, obsessiv-kompulsiv lidelse, panikanfald, panik-  
angst, posttraumatisk stresslidelse, separationsangst, social fobi, specifik fobi,  
stof-induceret angstlidelse og angst pga. generel medicinsk tilstand; stofrela-  
terede lidelser og vanedannende adfærd (herunder stof-induceret delirium,  
10 vedvarende demens, persisterende amnestisk lidelse, psykotisk lidelse eller  
angstlidelse; tolerance, afhængighed eller abstinenser fra stoffer, herunder alkohol, amfetamin, cannabis, kokain, hallucinogener, inhalatorer, nikotin, opio-  
ider, phencyclidin, beroligende midler, hypnotika eller anxiolytika); spisefor-  
styrrelser såsom fedme, bulimia nervosa, pica og kompulsive spiseforstyrrel-  
15 ser; bipolar lidelse, herunder bipolar I lidelse, bipolar II lidelse, cyklotymisk li-  
delse, stof/medicin-induceret bipolar og beslægtede lidelser, bipolar og be-  
slægtet lidelse på grund af en anden medicinsk tilstand, anden specificeret  
bipolar og beslægtet lidelse, og uspecificerede bipolare og beslægtede lidel-  
ser, depressiv lidelser, herunder unipolar depression, sæsonbestemt depres-  
20 sion og post-partum depression, atypisk depression, katatonisk depression,  
ældre depression, endogen depression, melankolsk depression, perinatal de-  
pression, situationel depression, kronisk depression, præmenstruelt syndrom  
(PMS) og præmenstruel dysforisk lidelse (PDD), humørforstyrrelser på grund  
af en generel medicinsk tilstand og stof-inducerede humørsygdomme; op-  
25 mærksomheds-, indlærings- og udviklingsforstyrrelser såsom gennemgri-  
bende udviklingsforstyrrelser, herunder autistisk lidelse, opmærksomhedsfor-  
styrrelser, herunder opmærksomheds- og hyperaktivitetsforstyrrelse (ADHD)  
og adfærdsforstyrrelser, lidelser såsom autisme og autismespektrumforstyrrel-  
ser, herunder Aspergers syndrom, gennemgribende udviklingsforstyrrelse,  
30 Rett syndrom og Fragile X-syndrom, depression, godartet glemsomhed, ind-

læringsforstyrrelser i barndommen, specifikke indlæringsforstyrrelser, intellektuelle udviklingsforstyrrelser, og lukket hovedskade; bevægelsesforstyrrelser og symptomer, herunder rysten, dyskinesi, dystoni, tics, dysfoni, ataksi, myoklonus, essentiel tremor, tardiv dyskinesi, rastløse ben-syndrom, Tourettes syndrom, multipel systematrofi, multipel sklerose, Huntingtons sygdom, Parkinsons og atypisk Parkinsons sygdom; epilepsi; urininkontinens; neuronal skade, herunder øjenskade, retinopati eller makuladegeneration af øjet, tinnitus, hørenedsættelse og -tab og hjerneødem; emesis; og søvnforstyrrelser, herunder søvnsløshed, forstyrret søvn, jetlag, hypersomni, katapleksi, søvn-apnø, obstruktiv søvnapnia, REM-søvnadfærdsforstyrrelse, rastløse ben-syndrom, periodisk bevægelsesforstyrrelse i lemmer, søvnforstyrrelser i døgnrytme, forsinket søvnfaseforstyrrelse, søvngængeri, natrædsler, sengevædning, hurtige øjenbevægelser søvnadfærdsforstyrrelser, søvnforstyrrelser på skifteholdsarbejde, overdreven søvnighed i dagtimerne, ikke-24-timers søvnvågen lidelse, søvnparalyse og narkolepsi; eller:

5 d) Alzheimers sygdom, Parkinsons sygdom, depression, kognitiv svækkelse, slagtilfælde, skizofreni, Downs syndrom eller førtalt alkoholsyndrom;

10 e) bipolar lidelse, herunder bipolar I og bipolar II; eller:

15 f) skizofreni, herunder paranoid skizofreni, uorganiseret skizofreni, katatonisk skizofreni eller udifferentieret skizofreni; eller:

20 g) angstlidelse, herunder separationsangst, selektiv mutisme, specifik fobi, social angstlidelse (social fobi), panikangst, panikanfaldsspecifikator, agorafobi, generaliseret angstlidelse, stof/medicin-induceret angstlidelse, angstlidelse på grund af en anden medicinsk tilstand, sygdomsangst, social (pragmatisk) kommunikationsforstyrrelse, anden specificeret angstlidelse og uspecificeret angstlidelse; stressor-relaterede lidelser, herunder reaktiv tilknytningsforstyrrelse, disinhiberet socialt engagementsforstyrrelse, posttraumatisk stresslidelse (PTSD), akut stressforstyrrelse og tilpasningsforstyrrelser; eller:

25 h) kognitiv svækkelse, herunder et fald i kognitive funktioner eller kognitive domæner, f.eks. arbejdshukommelse, opmærksomhed og årvågenhed, verbal indlæring og hukommelse, visuel læring og hukommelse, ræsonnement og

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problemløsning (f.eks. eksekutiv funktion, bearbejdningshastighed og/eller social kognition).

**31.** Forbindelse eller farmaceutisk acceptabelt salt deraf eller sammensætning til anvendelse i en fremgangsmåde ifølge krav 29 eller 30, hvor den neurologiske eller psykiatriske sygdom eller lidelse er:

a) paranoid skizofreni, uorganiseret skizofreni, katatonisk skizofreni eller udifferentieret skizofreni; eller:

b) skizoid personlighedsforstyrrelse eller skizotyp personlighedsforstyrrelse; eller:

c) alvorlig depression eller posttraumatisk stresssyndrom; eller:

d) semantisk demens, frontotemporal demens, demens med depressive træk, vedvarende, subkortikal demens, demens med Lewy Bodies, Parkinsonism-ALS Demens Complex, demens forbundet med Alzheimers sygdom, iskæmi, multi-infarkt demens, traumer, vaskulære problemer, slagtilfælde, HIV-sygdom, Parkinsons sygdom, Huntingtons sygdom, Downs syndrom, Picks sygdom, Creutzfeldt-Jacobs sygdom, perinatal hypoxi eller stofmisbrug; eller:

e) mangel på dopaminsignalering, dysfunktion af basalganglier, dysreguleret bevægelsesaktivitet eller svækelse af præfrontal cortex funktion; eller:

f) reaktiv tilknytningsforstyrrelse eller disinhiberet socialt engagementsforstyrrelse; eller:

g) fedme, bulimia nervosa, pica eller kompulsive spiseforstyrrelser; eller:

h) bipolar I lidelse, bipolar II lidelse, mani, cyklotymisk lidelse, stof/medicin-inducerede bipolære og beslægtede lidelser, bipolar og beslægtet lidelse på grund af en anden medicinsk tilstand, anden specifiseret bipolar og beslægtet lidelse eller uspecificerede bipolære og beslægtede lidelser; eller:

i) autistisk lidelse, autismespektrumforstyrrelse, opmærksomhedsforstyrrelser, opmærksomheds- og hyperaktivitetsforstyrrelse (ADHD), godartet glemsomhed, indlæringsforstyrrelser i barndommen, specifikke indlæringsforstyrrelser, intellektuelle udviklingsforstyrrelser eller lukket hovedskade.

**32.** Forbindelse ifølge et hvilket som helst af kravene 1 til 26, eller et farmaceutisk acceptabelt salt deraf, eller en sammensætning ifølge krav 27, til anvendelse i en fremgangsmåde til behandling af neuropsykiatriske symptomer og adfærdssymptomer i en neurologisk sygdom eller lidelse hos et individ, hvor fremgangsmåden omfattende indgivelse til individet af en effektiv mængde af forbindelsen; eventuelt hvor:

a) den neurologiske sygdom eller lidelse er valgt blandt Alzheimers sygdom og Parkinsons sygdom; eller:

b) den neurologiske sygdom eller lidelse er Alzheimers sygdom med agitation,

10 Alzheimers sygdom med aggression eller Alzheimers sygdom med agitation og aggression.

**33.** Forbindelse, farmaceutisk acceptabelt salt deraf eller sammensætning til anvendelse ifølge krav 32, hvor sygdommen eller lidelsen er:

15 a) humørsygdomme, herunder bipolar I lidelse, bipolar II lidelse, mani, cyklotymisk lidelse, stof/medicin-inducerede bipolære og beslægtede lidelser, bipolar og beslægtet lidelse på grund af en anden medicinsk tilstand, anden specificeret bipolar og beslægtet lidelse, og uspecificeret bipolar og relaterede lidelser; psykotiske lidelser, herunder skizofreni, skizofreni-spektrum-forstyrrelse, akut skizofreni, kronisk skizofreni, NOS skizofreni, skizoid personlighedsforstyrrelse, skizotypal personlighedsforstyrrelse, vrangforestillingsforstyrrelse, psykose, psykotisk lidelse, kortvarig psykotisk lidelse, fælles psykotisk lidelse, psykotisk lidelse på grund af en generel medicinsk lidelse tilstand, lægemiddelinduceret psykose, skizoaffektiv lidelse, agitation, aggression, delirium, katalepsi, katatoni, dissociativ identitetsforstyrrelse, paranoid personlighedsforstyrrelse, psykotisk depression, skizotypisk personlighedsforstyrrelse, disintegrativ barndomsforstyrrelse (Hellers syndrom), disintegrativ psykose, dissociativ hukommelsestab, somatisk symptomforstyrrelse, Parkinsons psykosesyndrom, excitativ psykose, Tourette's syndrom, and organisk eller

20 NOS psykose; depressive lidelser, herunder forstyrrende stemningsforstyrrelser, svær depressiv lidelse (MDD) inklusive svær depressiv episode, dystymi,

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vedvarende depressiv lidelse (dystymi), behandlingsresistent depression, præmenstruel dysforisk lidelse, stof/medicin-induceret depressiv lidelse, depressiv lidelse på grund af en anden medicinsk tilstand, anden specifiseret depressiv lidelse og uspecifiseret depressiv lidelse; angstlidelser; og andre lidelser, herunder stofmisbrug eller afhængighed, afhængighed, internetspilforstyrrelser, spiseforstyrrelser, adfærdsforstyrrelser, anfald, svimmelhed, epilepsi, agitation, aggression, neurodegenerativ sygdom, Alzheimers sygdom, Parkinsons sygdom, dyskinesier, Huntingtons sygdom, demens, præmenstruel dysfori, opmærksomhedsforstyrrelse (ADD) og opmærksomheds- og hyperaktivitetsforstyrrelse (ADHD), hyperkinetisk syndrom, autisme, autismespektrumforstyrrelse, obsessiv-kompulsiv lidelse, smerter, fibromyalgi, migrene, kognitiv svækkelse, bevægelsesforstyrrelse, rastløse bensyndrom (RLS), multipel sklerose, primær progressiv multipel sklerose, Parkinsons sygdom, Huntingtons sygdom, dyskinesiosis multipel sklerose, søvnforstyrrelse, søvnnapnø, narkolepsi, overdreven søvnighed i dagtimerne, jetlag, døsig bivirkning af medicin, søvnløshed, seksuel dysfunktion, hypertension, emesis, Lesche-Nyhane sygdom, Wilsons sygdom, Rett syndrom og Huntingtons chorea; eller:

b) obsessiv-kompulsiv lidelse og beslægtede lidelser, herunder kropsdysmorisk lidelse, hamstringslidelse, trikotillomani, excoriationslidelse; eller:

c) forstyrrende, impulskontrol- og adfærdsforstyrrelser, herunder oppositionel trodsig lidelse, intermitterende eksplosiv lidelse, adfærdsforstyrrelse, antisocial personlighedsforstyrrelse, pyromani, kleptomani, anden specifiseret forstyrrelse, impulskontrol og adfærdsforstyrrelse, uspecifiseret forstyrrende, impulskontrol, og adfærdsforstyrrelse; eller:

d) bevægelsessygdomme eller forstyrrelser, herunder akinesier, akinetisk-rigide syndromer, dyskinesier og dystonier, eventuelt hvor sygdommen eller lidelsen er Parkinsons sygdom, lægemiddelinduceret Parkinsonisme, postencephalitisk Parkinsonisme, sekundær Parkinsonisme, Parkinson plus syndromer, atypisk Parkinsonisme, idiopatisk Parkinsonisme, progressiv supranu-

kleær parese, multipel system atrofi, kortikobasal degeneration, Parkinsonisme-ALS demenskompleks og basalgangliaforkalkning, medicininduceret Parkinsonisme inklusive neuroleptika-induceret parkinsonisme, neuroleptika-induceret malignt syndrom, neuroleptika-induceret akut dystoni, neuroleptika-induceret akut akatisi og neuroleptikainduceret tardiv dyskinesi og medicininduceret postural tremor, Gilles de la Tourettes syndrom, epilepsi, muskelspærmer og lidelser forbundet med muskulær spasticitet eller svaghed, herunder rystelser, lægemiddelinduceret dyskinesi-tremor inklusive hvile-tremor, postural tremor, intentionel tremor, chorea inklusive Sydenhams chorea, Huntingtons sygdom, godartet arvelig chorea, neuroacanthocytose, symptomatisk chorea, lægemiddelinduceret chorea og hemiballisme, myoklonus inklusive generaliseret myoklonus og fokal myoklonus, tics inklusive simple tics, komplekse tics og symptomatiske tics, generaliseret dystoni, idiopatisk dystoni, lægemiddelinduceret dystoni, symptomatisk dystoni, paroxymal dystoni, fokal dystoni, blefarospasme, oromandibulær dystoni, spasmodisk dysfoni, spasmodisk torticollis, aksial dystoni, dystonisk forfatterkramper og hemiplegisk dystoni, stereotyp bevægelsesforstyrrelse, vedvarende (kronisk) motorisk lidelse, medicin-induceret bevægelsesforstyrrelse, psykogene bevægelsesforstyrrelser, stof/medicin-induceret bevægelsesforstyrrelse, ekstrapyramidale forstyrrelser, hyperkinetiske bevægelsesforstyrrelser, hypokinetiske bevægelsesforstyrrelser, alternerende hemiplegi, Angelmans syndrom, Hallervorden-Spatz sygdom, ataksi, dentate cerebellar ataksi, ataksi telangiectasia (Louis-Bar syndrom), Friedreichs ataksi, arvelig spinal ataksi, arvelig spinal sklerose, Machado-Joseph-sygdom, spinocerebellar ataksi, progressiv myoklonisk ataksi, athetose, ballismus, blefarospasme (øjentrækninger), cerebral parese, tardiv dystoni, tardiv dyskinesi, idiopatisk torsionsdystoni, torsionsdystoni, fokal dystoni, idiopatisk familiær dystoni, idiopatisk nonfamiliær dystoni, cervikal dystoni (spasmodisk torticollis), primær dystoni, orofacial dystoni, udviklingskoordinationsforstyrrelser, bulbospinal muskelatrofi (Kennedys sygdom), Shy-Drager syndrom og Stiff-Person (Stiff-Man) syndrom; eller:  
e) abdominal epilepsi, fraværsanfald, erhvervet epilepsi, erhvervet epileptiform

afasi, Aicardi syndrom, Alpers' sygdom, Alpers-Huttenlocher syndrom, Angelman syndrom, benign fokal epilepsi, benign fokal epilepsi i barndommen, benign intrakraniel hypertension, benign rolandisk epilepsi (BRE), CDKL5 lidelse, fraværsepilepsi i barndommen, dentat cerebellar ataksi, Doose syndrom, Dravet syndrom, dysognitivt fokalt anfall, epilepsi med grand mal-anfall, epilepsi med myokloniske fravær, epileptisk hemiplegi, febrile anfall, fokale anfall, frontal-lobe epilepsianfall, generaliserede tonisk-kloniske anfall, genetisk epilepsi, Glut1-mangelsyndrom, hypothalmisk hamartom, idiopatisk epilepsi, idiopatisk generaliseret epilepsi, idopatisk lokaliseringrelaterede epilepsier, idopatisk partiel epilepsi, idopatisk anfall, juvenil fraværsepilepsi, juvenil myoklonisk sygdom, Lafora epilepsi, Lafora progressiv myoklonus-epilepsi, Landau-Kleffners syndrom, Lassueur-Graham-Little syndrom, Lennox syndrom, Lennox-Gastaut syndrom, medicinsk refraktær epilepsi, mesial-temporal lap sklerose, myoklonisk anfall, neonatal epilepsi, occipitallapsepilepsi, Ohtahara-syndrom, Panayiotopoulos-syndrom, parietallapsepilepsi, PCDH19 epilepsi, lysfølsom epilepsi, progressive myokloniske epilepsier, Rasmussens encephalitis, Rasmussens syndrom, refraktær epilepsi, krampeanfall, status epilepticus, Sturge-Weber syndrom, symptomatisk generaliseret epilepsi, symptomatisk parital epilepsi, TBCK-relateret ID-syndrom, temporallapsepilepsi, temporallapsanfall, tonisk-klonisk anfall, West syndrom, tremor, cerebellar tremor, cerebellar udstrømningstremor, intentionel tremor, essentiel tremor, benign essentiel tremor, Parkinson tremor og medicin-induceret postural tremor.

25           **34.** Forbindelse, farmaceutisk acceptabelt salt deraf eller sammensætning til anvendelse ifølge krav 32, hvor symptomet er:

20           a) depression, herunder svær depressiv lidelse eller dystymi; bipolar lidelse, sæsonbestemt affektiv lidelse; kognitivt underskud; søvnrelateret lidelse, såsom søvnnapnø, søvnsløshed, narkolepsi, katapleksi, herunder de søvnforstyrrelser, som frembringes af psykiatriske tilstande; kronisk træthedssyndrom;

angst, herunder generel angstlidelse, social angstlidelse, panikangst; obses-siv-kompulsiv lidelse; postmenopausale vasomotoriske symptomer, herunder hedeture, nattesved; neurodegenerativ sygdom, herunder Parkinsons sygdom, Alzheimers sygdom, amyotrofisk lateral sklerose, primær lateral skle-  
5 rose, progressiv muskelatrofi, progressiv bulbar (atrofi) parese, pseudobulbar parese spinal muskelatrofi-sygdomme, herunder SMA type I, også kaldet Werdnig-Hoffmanns sygdom, SMA type II, SMA type III, også kaldet Kugel-berg-Welander sygdom, og Kennedy Sygdom, også kaldet progressiv spinobulbar muskelatrofi, Hallervorden-Spatz sygdom, Seitelberger sygdom (in-fantil neuroaksonal dystrofi), adrenoleukodystrofi, Alexander sygdom, autosomal dominant cerebellar ataksi (ADCA), ren autonom svigt (Bradbury-Eggle-ston Syndrome), CADASII, Syndrome, og neuronale ceroider lipofuscinose lidelser såsom Batten Disease (Spielmeyer-Vogt-Sjögren)); manisk lidelse; dysthymisk lidelse; og fedme; eller:

10 b) senil demens, tidligt opstået Alzheimers sygdom, Alzheimers type demens, kognition, hukommelsestab, amnesi/amnestisk syndrom, bevidsthedsforstyr-relser, koma, nedsat opmærksomhed, taleforstyrrelser, agnosi, afasi, apraksi, mild kognitiv svækkelse (MCI), godartet glemsomhed, mild neurokognitiv lidelse, større neurokognitiv lidelse, neurokognitiv lidelse på grund af sygdom, herunder Huntingtons sygdom, Parkinsons sygdom, Prion sygdom, traumatiske  
20 hjerneskade, HIV eller AIDS, Binswangers sygdom (subkortikal leukoencefalo-pati) og Capgras syndrom; eller:

25 c) smerte, herunder neuropatisk smerte, sensibilisering, der ledsager neuropatisk smerte, eller inflammatorisk smerte, eventuelt hvor smerten er posther-petisk (eller post-helvedesild) neuralgi, refleks-sympatisk dystrofi/kausalgi el-ler nervetraume, fantomlemmesmerter, karpaltunnelsyndrom, perifert neuro-pati, herunder diabetisk neuropati eller neuropati som følge af kronisk alkohol-brug, akutte smerter, nociceptive smerter, gigtsmerter, reumatoid arthritis, slid-gigt, ledsmarter, muskoskeletale smerter, rygsmarter, dorsalgi, svulmende diskus, hofte-smerter, viscerale smerter, hovedpine, spændingshovedpine,

akut spændingshovedpine, kronisk spændingshovedpine, kronisk klyngehovedpine, almindelig migræne, klassisk migræne, klyngehovedpine, blandet hovedpine, posttraumatisk hovedpine, øjenbelastningshovedpine, kortvarig unilateral neuralgiform (SUNCT) hovedpine, SUNCT syndrom, herpes zoster,  
5 akut herpes zoster, helvedesild, postherpetisk neuralgi (helvedesild), kausalgi, central smerte, central smertesyndrom, kroniske rygsmerter, neuralgi, neuropatisk smertesyndrom, neuropati, diabetisk neuropati, diabetesrelateret neuropati, diabetesrelateret nervesmerter, fibrosis, perifer neuropati forårsaget af kemoterapi, perifer nervesygdom, perifer neuropati, nervesmerter, nervetrau-  
10 mer, sensibilisering, der ledsager neuropatisk smerte, komplekst regionalt smertesyndrom, kompressionsneuropati, kraniofacial smerte, kroniske led-  
smerter, kroniske knæsmerter, kronisk smertesyndrom, kræftsmarter, trigemiusneuralgi, tic doloreaux, refleks-sympatisk kausalgi, smertefuld perifer neuropati, spinal nerveskade, arachnoiditis, spinal smerte, Bernhardt-Roth syndrom (meralgia parasthetica), karpaltunnelsyndrom, cerebrospinalvæske-syndrom, Charcot-Marie-tandsygdom, arvelig motorisk og sensorisk neuropati, peroneal muskelatrofi, klynge-tic syndrom, coccygeal smerte syndromer, kom-  
15 partment syndrom, degenerativ diskus-sygdom, mislykket rygkirurgisyndrom, genito-bækken-smerte/penetrationslidelse, gigt, inflammatorisk smerte, lum-  
bal radikulopati, neuroma (smertefuld ar), smerter forbundet med multiple sklerose, bækkenbundsforstyrrelser, fantomsmerter, piriformis syndrom, psy-  
20 kogen smerte, radikulært smertesyndrom, Raeders syndrom, refereret smerte, refleks sympathisk dystrofisyndrom, iskias, iskiassmerter, skoliose, diskuspro-  
laps, somatisk smerte, spinal stenose, stiff-person syndrom/stiff-man syndrom, stumpsmerter, sympathisk vedligeholdte smerter, tolosa-hunt syndrom, piske-  
25 smæld eller smerte forbundet med borreliose; eller:  
d) fedme; migræne eller migrænehovedpine; og seksuel dysfunktion, hos mænd eller kvinder, herunder uden begrænsning seksuel dysfunktion forårsa-  
get af psykologiske og/eller fysiologiske faktorer, erektil dysfunktion, for tidlig sædafgang, vaginal tørhed, mangel på seksuel ophidselse, manglende evne  
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til at opnå orgasme og psykoseksuel dysfunktion, herunder uden begrænsning, hæmmet seksuel lyst, hæmmet seksuel ophidselse, hæmmet kvindelig orgasme, hæmmet mandlig orgasme, funktionel dyspareuni, funktionel vaginisme og atypisk psykoseksuel dysfunktion; eller:

5 e) katapleksi; nattesøvnforstyrrelser/søvnfragmentering forbundet med narkolepsi eller andre tilstande; søvnparalyse forbundet med narkolepsi eller andre tilstande; hypnagogiske og hypnapompiske hallucinationer forbundet med narkolepsi eller andre tilstande; og overdreven søvnighed i dagtimerne forbundet med narkolepsi, søvnnapnø eller skifteholdsforstyrrelser og andre medicinske tilstande, herunder cancer, kronisk træthedssyndrom og fibromyalgi.

10 35. Forbindelse, farmaceutisk acceptabelt salt deraf eller sammensætning til anvendelse ifølge krav 32, hvor symptomet er valgt blandt:

a) et fald i kognitive funktioner eller kognitive domæner; eller:

15 b) underskud i opmærksomhed, uorganiseret tænkning, langsom tænkning, vanskeligheder med at forstå, dårlig koncentration, svækkelse af problemløsning, dårlig hukommelse, vanskeligheder med at udtrykke tanker; vanskeligheder med at integrere tanker, følelser og adfærd, eller vanskeligheder med at utslette irrelevante tanker; eller:

20 c) underskud i dopaminsignalering; eller:

d) rysten, dyskinesi, dystoni, tics, dysfoni, ataksi eller myoklonus; eller:

e) bipolar lidelse, sæsonbestemt affektiv lidelse; kognitiv deficit, søvnrelateret lidelse, søvnforstyrrelse frembragt af psykiatriske tilstande, kronisk træthedssyndrom, angst, obsessiv-kompulsiv lidelse, postmenopausale vasomotoriske 25 symptomer, neurodegenerativ sygdom, manisk lidelse, dysthymisk lidelse eller fedme; eller:

f) senil demens, tidligt opstået Alzheimers sygdom, Alzheimers type demens, kognition, hukommelsestab, amnesi/amnestisk syndrom, bevidsthedsforstyrrelser, koma, nedsat opmærksomhed, taleforstyrrelser, agnosi, afasi, apraksi, 30 mild kognitiv svækkelse (MCI), godartet glemsomhed, mild neurokognitiv lidelse, større neurokognitiv lidelse, neurokognitiv lidelse på grund af sygdom,

Binswangers sygdom (subkortikal leukoencefalopati) eller Capgras syndrom; eller:

g) smerte; eller:

h) migræne eller migrænehovedpine eller seksuel dysfunktion; eller:

5 i) nattesøvnforstyrrelser/søvnfragmentering forbundet med narkolepsi eller andre tilstænde; søvnparalyse forbundet med narkolepsi eller andre tilstænde, hypnagogiske og hypnapompiske hallucinationer forbundet med narkolepsi eller andre tilstænde, eller overdreven søvnighed i dagtimerne forbundet med narkolepsi, søvnnapnø eller skifteholdsforstyrrelser og andre medicinske tilstande; eller:

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j) akinesier, akinetisk-stive syndromer, dyskinesier eller dystonier; eller:

k) apati, depression, kognitiv svækkelse, psykose, aggression, agitation, dårlig impulskontrol eller søvnforstyrrelser; eller:

l) forstyrrelser i opfattelse, tankeindhold, humør eller adfærd; eller:

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m) forhøjet eller irritabelt humør, hyperaktivitet, grandiositet, nedsat søvnbehov, travle tanker og psykose, anhedoni, trist humør, håbløshed, dårligt selv-værd, nedsat koncentrationsevne eller sløvhed; eller:

n) forstyrrelser i tankeindhold, mentalitsforstyrrelser, sanselighedsforstyrrelser, følelser, selvopfattelser, intentioner, impulser og/eller inter-menneskelige forhold eller psykomotoriske lidelser; eller:

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o) frygt, bekymring eller uro; eller:

p) deprimeret humør, dårlig koncentration, søvnsløshed, træthed, appetitforstyrrelser, overdreven skyldfølelse eller selvmordstanker.

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**36.** Forbindelse, farmaceutisk acceptabelt salt eller sammensætning ifølge krav 35, hvor

a) de kognitive funktioner og kognitive domæner er udvalgt fra arbejdshukommelse, opmærksomhed og årvågenhed, verbal indlæring og hukommelse, visuel indlæring og hukommelse, ræsonnement og problemløsning; eller:

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b) den søvnrelaterede lidelse er valgt blandt søvnnapnø, søvnsløshed, narkolepsi og katapleksi; eller:

c) angst er valgt blandt generel angstlidelse, social angstlidelse og panikangst; eller:

d) det postmenopausale vasomotoriske symptom er valgt blandt hedeture og nattesved; eller:

5 e) den neurodegenerative sygdom er udvalgt blandt Parkinsons sygdom, Alzheimers sygdom, amyotrofisk lateral sklerose, primær lateral sklerose, progressiv muskelatrofi, progressiv bulbar (atrofi) parese, pseudobulbar parese-spinal-muskelatrofi-sygdomme, Hallervorden-Spatz sygdom, Seitelbergers sygdom (infantil neuroaksonal dystrofi), adrenoleukodystrofi, Alexanders sygdom, autosomal dominant cerebellar ataksi (ADCA), ren autonom svigt (Bradbury-Eggleston syndrom), CADASII, syndrom og neuronale ceroider lipofuscinoselidelser; eller:

10 f) den neurokognitive lidelse på grund af sygdom er valgt blandt Huntingtons sygdom, Parkinsons sygdom, Prion sygdom, traumatisk hjerneskade, HIV eller AIDS; eller:

15 g) nævnte smerte er udvalgt blandt neuropatisk smerte, sensibilisering, der ledsager neuropatisk smerte, inflammatorisk smerte, akut smerte, nociceptiv smerte, gigtsmerter, leddegit, slidigt, ledsmærter, muskoskeletale smerter, rygsmærter, dorsalgi, svulmende diskus, hoftesmerter, visceral smerte, hovedpine, spændingshovedpine, akut spændingshovedpine, kronisk spændingshovedpine, kronisk klyngehovedpine, almindelig migræne, klassisk migræne, klyngehovedpine, blandet hovedpine, posttraumatisk hovedpine, øjenbelastningshovedpine, kortvarig unilateral neuralgiform (SUNCT) hovedpine, SUNCT syndrom, herpes zoster, akut herpes zoster, helvedesild, postherpetisk neuralgi ( helvedesild), kausalgi, central smerte, central smertesyndrom, kroniske rygsmærter, neuralgi, neuropatisk smertesyndrom, neuropati, diabetisk neuropati, diabetesrelateret neuropati, diabetesrelateret nervesmerter, fibrositis, perifer neuropati forårsaget af kemoterapi, perifer nervesygdom, perifer neuropati, nervesmerter, nervetraume, sensibilisering, der ledsager regional neuropatisk smerte, kompleks regional smertesyndrom, kompressionsneuropati, kraniofacial smerte, kroniske ledsmerte, kroniske knæsmerte, kronisk

smertesyndrom, cancersmerter, trigeminusneuralgi, tic doloreaux, refleks sympathisk kausalgi, smertefuld perifer neuropati, spinal nerveskade, arachnoiditis, spinal smerte, Bernhardt-Roth syndrom (meralgia carpalasthetica), carpal tunnelsyndrom, cerebrospinalvæske syndrom, Charcot-Marie-tandsyndrom, arvelig motorisk og sensorisk neuropati, peroneal muskelatrofi, klyngetic syndrom, coccygeal smertesyndromer, kompartment syndrom, degenerativ diskussygdom, mislykket rygkirurgisyndrom, genito-bækken smerte/penetrationslidelse, gigt, inflammatoriske smerter, lumbal radikulopati, neuromer (smertefuldt ar), smerter forbundet med flere sklerose, bækkenbundslidelser, fantomsmerter i lemmer, piriformis syndrom, psykogen smerte, radikulær smerte-syndrom, Raeders syndrom, refereret smerte, refleks sympathisk dystrofisyndrom, iskias, iskiassmerter, skoliose, diskusskred, somatisk smerte, spinal stenos, stiff-person-syndrom/stiff-man-syndrom, stumpesmerter, sympathisk vedligeholdte smerter, tolosa-hunt syndrom, piskestmæld og smerte forbundet med borreliose; eller:

h) den seksuelle dysfunktion er valgt blandt seksuel dysfunktion forårsaget af psykologiske og/eller fysiologiske faktorer, erektil dysfunktion, for tidlig ejakulation, vaginal tørhed, mangel på seksuel ophidselse, manglende evne til at opnå orgasme, psykoseksuel dysfunktion; eller:

i) nævnte akinesier og akinetisk-rigide syndromer er udvalgt blandt Parkinsons sygdom, lægemiddelinduceret Parkinsonisme, postencephalitisk Parkinsonisme, sekundær Parkinsonisme, Parkinson plus syndromer, atypisk Parkinsonisme, idiopatisk Parkinsonisme, progressiv supranukleær parese, multipel systematrofi, kortikobasal degeneration, Parkinson-ALS-demenskompleks og basal gangliaforkalkning, medicin-induceret Parkinsonisme, Gilles de la Tourettes syndrom, epilepsi og muskelspasmer og lidelser forbundet med muskelspasticitet eller -svaghed; eller:

j) nævnte dyskinesier og dystonier er udvalgt blandt lægemiddel-induceret dyskinesi tremor, chorea, myoklonus, tics, generaliseret dystoni, idiopatisk dystoni, lægemiddel-induceret dystoni, symptomatisk dystoni, paroxymal dystoni, fokal dystoni, blefarospasme, oromandibulær dystoni, spasmodisk

dystoni, spasmodisk torticollis, aksial dystoni, dystonisk forfatterkrampe, hemiplegisk dystoni, stereotyp bevægelsesforstyrrelse, vedvarende (kronisk) motorisk lidelse, medicin-induceret bevægelsesforstyrrelse, psykogene bevægelsesforstyrrelser, stof/medicin-induceret bevægelsesforstyrrelse, ekstrapyramidale bevægelsesforstyrrelser, hyperkinetiske bevægelsesforstyrrelser, hypokinetiske bevægelsesforstyrrelser, alternerende hemiplegi, Angelman syndrom, Hallervorden-Spatz sygdom, ataksi, dentate cerebellar ataksi, ataxia telangiectasia (Louis-Bar syndrom), Friedreichs ataksi, arvelig spinal ataksi, arvelig spinal sklerose, Machado-Joseph sygdom, spinocerebellar ataksi, progressiv myoklonisk ataksi, athetos, ballisme, blefarospasme (trækninger i øjnene), cerebral parese, tardiv dystoni, tardiv dyskinesi, idiopatisk torsionsdystoni, torsionsdystoni, fokal dystoni, idiopatisk familiær dystoni, idiopatisk ikke-familiær dystoni, cervikal dystoni (spasmodisk torticollis), primær dystoni, orofacial dystoni, udviklingsmæssig koordinationsforstyrrelse, bulbospinal muskelatrofi (Kennedys sygdom), Shy-Drager-syndrom og Stiff-Person (Stiff-Man) Syndrom; eller:

k) nævnte epilepsi og anfall er udvalgt blandt abdominal epilepsi, fraværsanfall, erhvervet epilepsi, erhvervet epileptiform afasi, Aicardi syndrom, Alpers' sygdom, Alpers-Huttenlocher syndrom, Angelman syndrom, benign fokal epilepsi, benign fokal epilepsi hos børn, godartet rolandsk epilepsi (BRE), CDKL5 lidelse, fraværsepilepsi i barndommen, dentat cerebellar ataksi, Doose syndrom, Dravet syndrom, dyscognitive fokale anfall, epilepsi med grand mal-anfall, epilepsi med myokloniske fravær, epileptisk hemiplegi, febrile anfall, fokalt anfall, frontallapepilepsi, generaliseret tonisk-kloniske anfall, genetisk epilepsi, Glut1-mangelsyndrom, hypotalmisk hamartom, idiopatisk epilepsi, idiopatisk generaliseret epilepsi, idiopatisk lokaliseringsrelaterede epilepsier, idiopatisk partiel epilepsi, idiopatisk anfall, juvenil fraværsepilepsi, juvenil epilepsi, Lafora sygdom, Lafora progressiv myoklonus epilepsi, Landau-Kleffner syndrom, Lassueur-Graham-Little syndrom, Lennox syndrom, Lennox-Gastaut syndrom, medicinsk refraktær epilepsi, mesial-temporal lap-sklerose,

myoklonsk anfall, neonatal epilepsi, epilepsi i occipitallappen, Ohtahara syndrom, Panayiotopoulos syndrom, parietallapepilepsi, PCDH19 epilepsi, lysfølsom epilepsi, progressive myokloniske epilepsier, Rasmussens encephalitis, Rasmussens syndrom, refraktær epilepsi, krampeanfall, status epilepticus, 5 Sturge-Weber syndrom, symptomatisk generaliseret epilepsi, symptomatisk partiell symptomatisk epilepsi, TBCK-relateret ID-syndrom, tindingelappens epilepsi, tindingelappens anfall, tonisk-klonisk anfall, West syndrom, tremor, cerebellar tremor, cerebellar udstrømningstremor, intentionel tremor, essentiel tremor, benign essentiel tremor, Parkinson tremor og medicininduceret postural tremor ; eller:

10 l) nævnte forstyrrelser i opfattelse, tankeindhold, humør eller adfærd er udvalgt fra vrangforestillinger, hallucinationer, agitation, fysisk og/eller verbal aggression, depression eller dysfori, angst, apati eller ligegyldighed, uhæmmethed, motorisk forstyrrelse, impulsivitet, opmærksomhedsforstyrrelser, og eksekutiv 15 dysfunktion; eller:

m) de psykotiske symptomer er udvalgt fra multiple, fragmentariske, usammenhængende, usandsynlige eller blot vrangforestillinger; ideer om forfølgelse; tab af association, fantasiflukt, usammenhængende op til uforståelighed; hallucinationer; overfladiske eller utilstrækkelige følelser; og katatoni.

20 **37.** Forbindelse ifølge et hvilket som helst af kravene 1 til 26, eller et farmaceutisk acceptabelt salt deraf, eller en sammensætning ifølge krav 27, til anvendelse til at undertrykke hurtige øjenbevægelser (REM) under både søvn og dagtidsækvivalent i et individ med behov derfor.

25 **38.** Forbindelse ifølge et hvilket som helst af kravene 1 til 26, eller et farmaceutisk acceptabelt salt deraf, eller en sammensætning ifølge krav 27, til anvendelse til at undertrykke eller eliminere patologisk eller overdreven REM i løbet af natten eller dagtimerne i et individ med behov derfor.

# DRAWINGS

Drawing

**FIGURE 1a**

Compound of Example 2

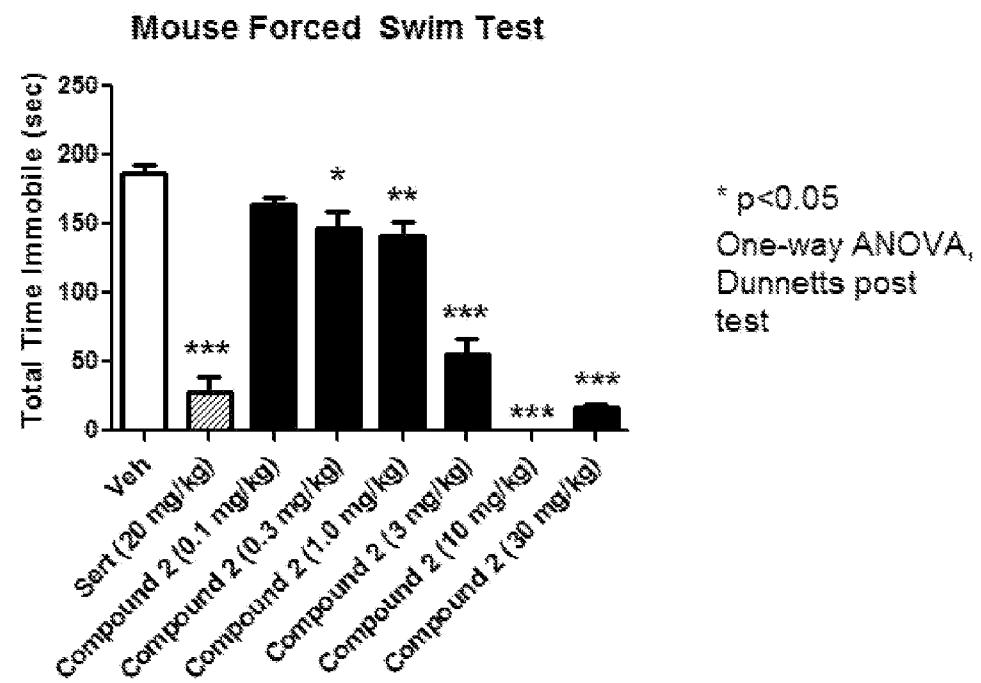


Figure 1b  
Compound of Example 26

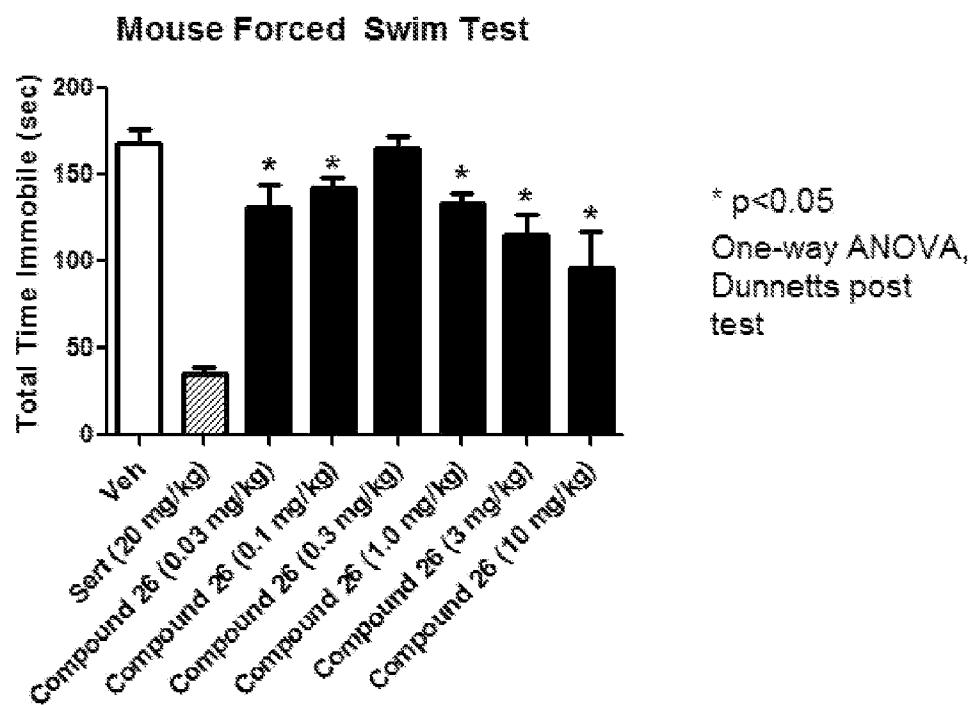


Figure 2a  
Compound of Example 2

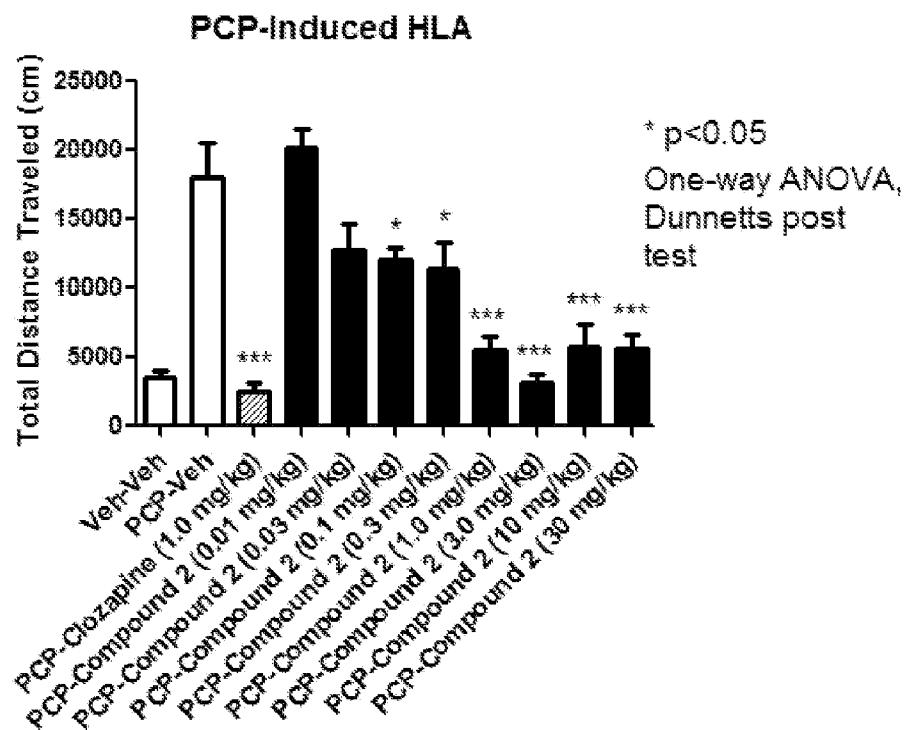


Figure 2b

## Compound of Example 26

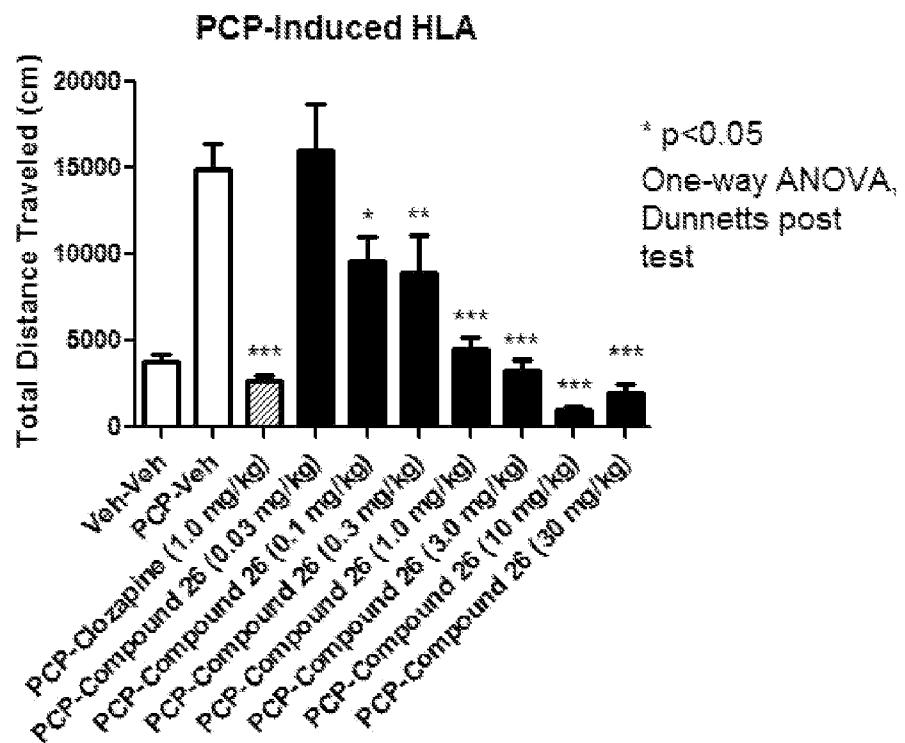


Figure 3a  
Compound of Example 2

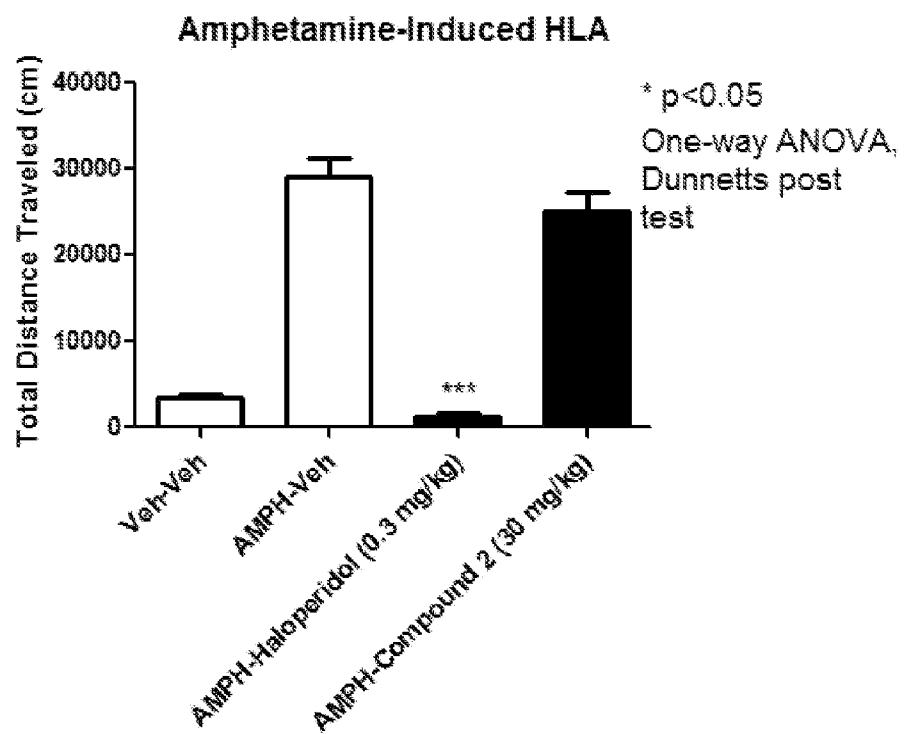


Figure 3b

## Compound of Example 14

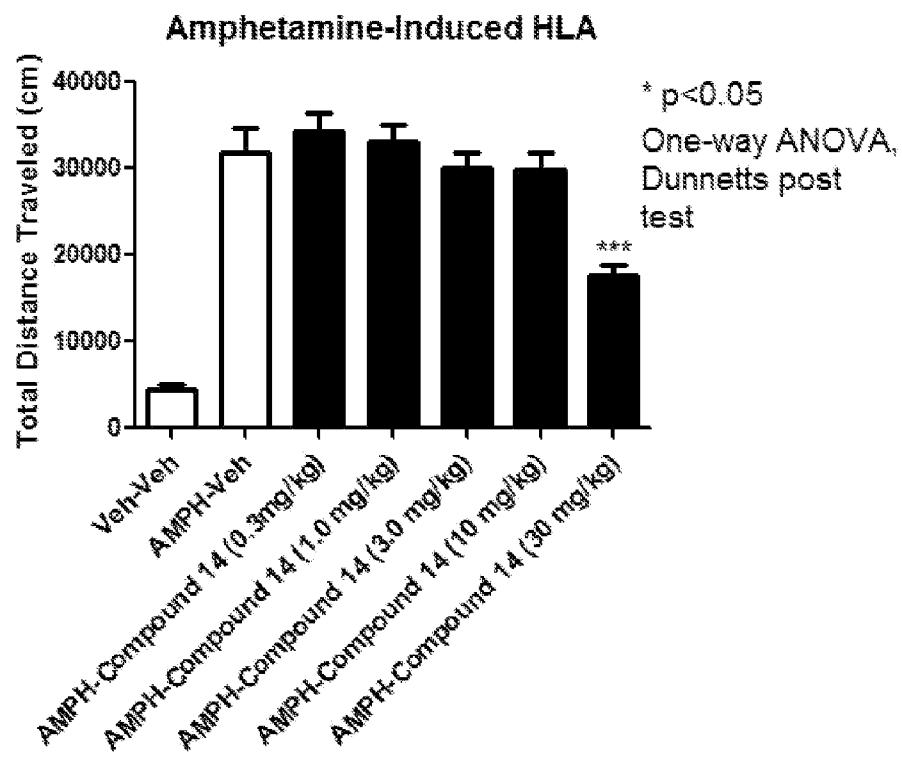


Figure 3c

## Compound of Example 17

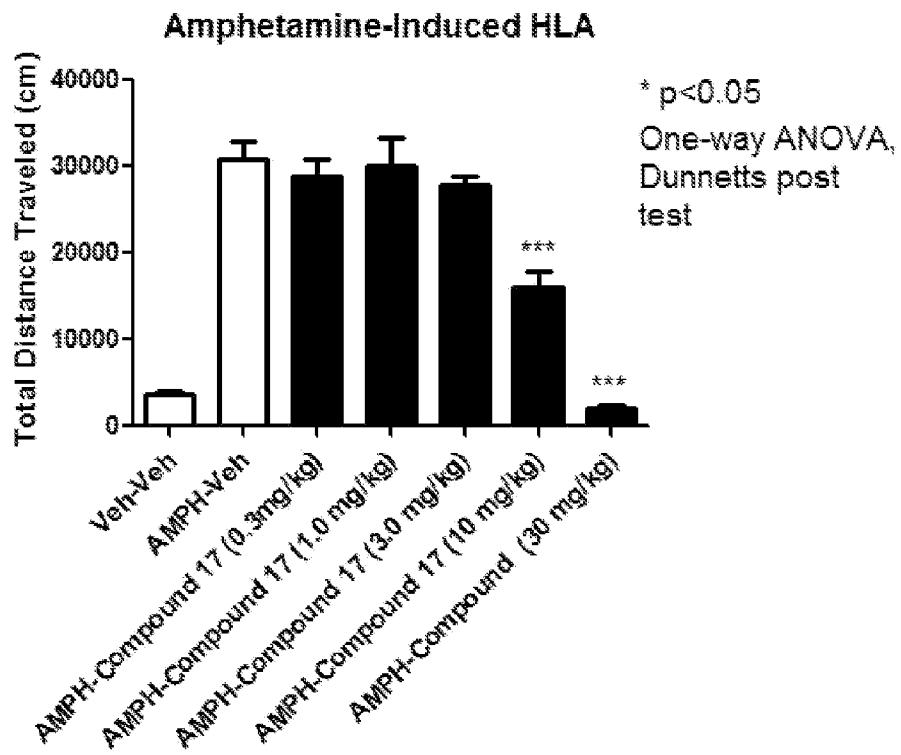


Figure 3d

## Compound of Example 26

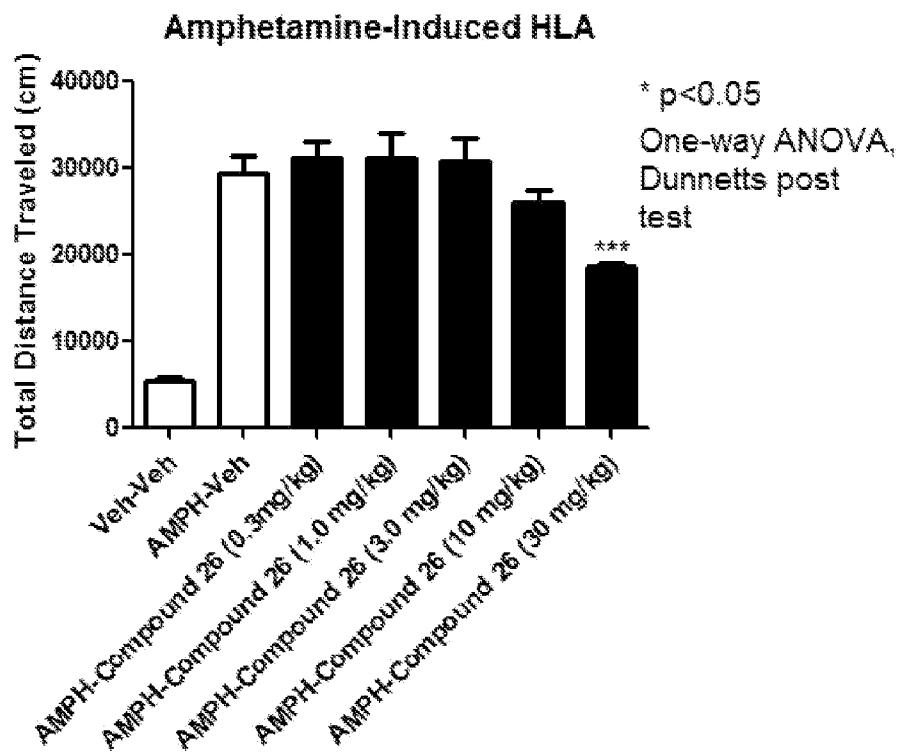


Figure 4a  
Compound of Example 14

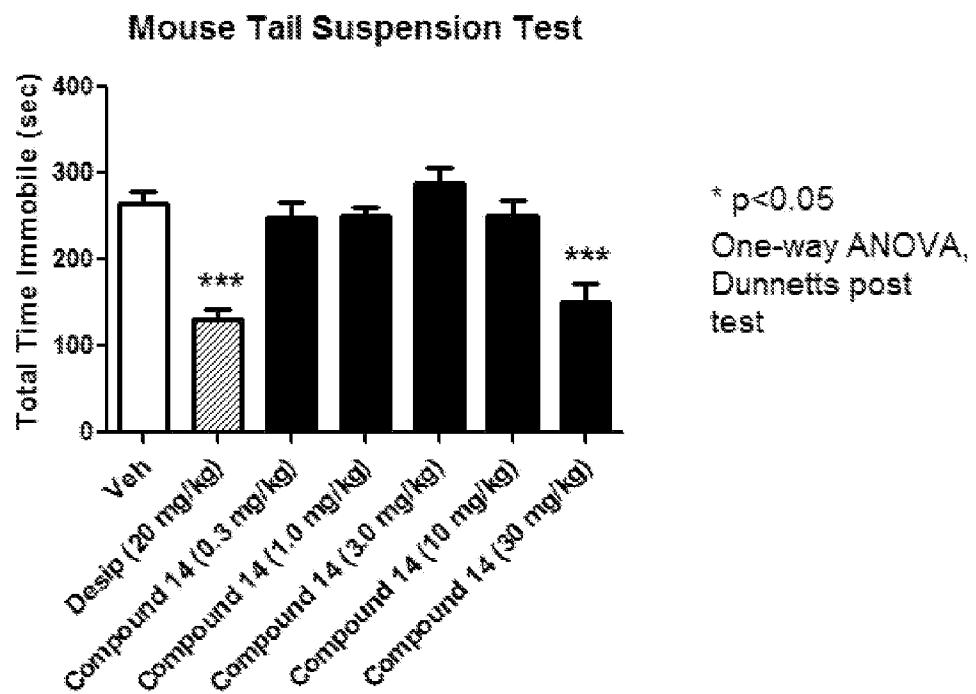


Figure 4b  
Compound of Example 17

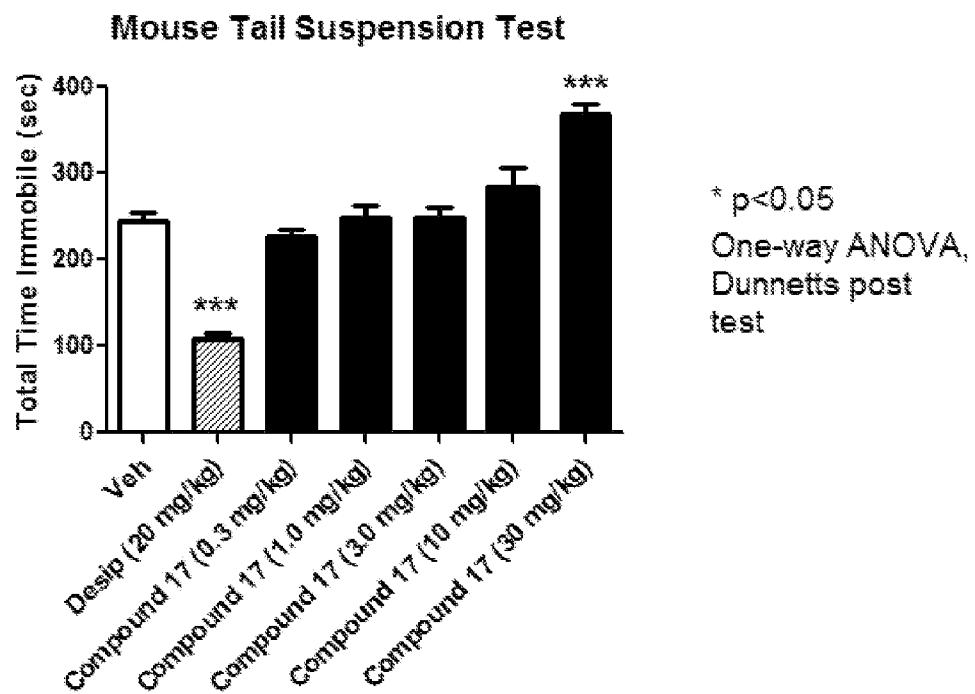


Figure 4c  
Compound of Example 26

